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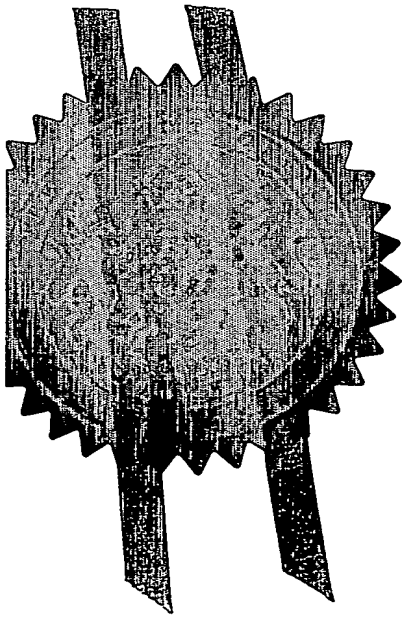

Signed

Dated 16 July 2003

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Patents Form 1/77

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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office
Cardiff Road
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NP9 1RH

1. Your reference
LRD-GB-2-415

10 JUN 2003

2. Patent application number
(The Patent Office will fill in this part)
0313251.1

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*
Rega Foundation, Minderbroedersstraat 10, 3000 Leuven
Represented by Prof. Dr. Erik De Clercq, President, Rega Foundation
Patents ADP number *(if you know it)* 78935790001

If the applicant is a corporate body, give the country/state of its incorporation Belgium

4. Title of the invention
Viral inhibitors

5. Name of your agent *(if you have one)*
"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*
K.U.Leuven R&D
care off:
Hubert Velge
Neaves Cottage
Neaves Lane - Glyndebourne
East Sussex BN8 5UA
Patents ADP number *(if you know it)* 80079160003

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*
a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))
Yes

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	43
Claim(s)	10
Abstract	1
Drawing(s)	0

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	2
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	1 fax cover sheet 1 fee sheet with request for fax back service

11. I/We request the grant of a patent on the basis of this application.

Prof. Dr. Erik De Clercq — Signature — Date 05 June 2003

12. Name and daytime telephone number of person to contact in the United Kingdom: Hubert Velge, +44 7940 540 397

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Notes

a) *If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.*

b) *Write your answers in capital letters using black ink or you may type them.*

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d) *If you have answered 'Yes' Patents Form 7/77 will need to be filed.*

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Viral inhibitors

FIELD OF THE INVENTION

The present invention relates to a series of novel imidazo[4,5-c]pyridine derivatives, processes for their preparation, their use to treat or prevent viral infections and their use to manufacture a medicine to treat or prevent viral infections, preferably infections with viruses belonging to the family of the Flaviviridae and more preferably infections with hepatitis-C-virus (HCV). The present invention also relates to the use of novel imidazo[4,5-c]pyridine derivatives to treat viral infections and their use to manufacture a medicine to treat viral infections, preferably infections with viruses belonging to the family of the Picornaviridae and more preferably infections with Coxsackie viruses.

BACKGROUND OF THE INVENTION

The family of the Flaviviridae consists of 3 genera, the pestiviruses, the flaviviruses and the hepaciviruses and also contains the hepatitis G virus (HGV/GBV-C) that has not yet been assigned to a genus. Pestiviruses such as the Classical Swine Fever Virus (CSFV), the Bovine Viral Diarrhea Virus (BVDV) and the Border Disease Virus (BDV) cause infections of domestic livestock (respectively pigs, cattle and sheep) and are responsible for significant economic losses worldwide. BVDV, the prototypic representative of the pestivirus genus is ubiquitous and causes a range of clinical manifestations, including abortion, teratogenesis, respiratory problems, chronic wasting disease, immune system dysfunction, and predisposition to secondary viral and bacterial infections and may also cause acute fatal disease. Fetuses of cattle can be infected persistently with BVDV, these animals remain viremic throughout life and serve as a continuous sources for virus spread in herds.

Vaccines are used in some countries with varying degrees of success to control pestivirus disease. In other countries, animal culling and slaughter are used to contain pestivirus disease outbreaks (Leyssen P, et al., Clin Microbiol Rev. 2000 Jan;13(1):67-82).

The World Health Organization estimates that world-wide 170 million people are chronically infected with HCV (Leyssen P, et al., Clin Microbiol Rev. 2000 Jan;13(1):67-82). These chronic carriers are at risk of developing cirrhosis and/or liver cancer. The only treatment

option available today is the use of (pegylated) interferon α-2 together with ribavirin. However, the response rate to this treatment is only partial and often transient and treatment is associated with serious adverse effects. The development of new and specific anti-HCV treatments is a high priority. The study of specific inhibitors of HCV replication has been hampered by the fact that it is not possible to propagate HCV (efficiently) in cell culture. Since HCV and pestiviruses belong to the same virus family and share many similarities (organisation of the genome, analogous gene products and replication cycle), pestiviruses have been adopted as a model and surrogate for HCV.

One compound VP32947 or (3-[((2-dipropylamino)ethyl)thio]-5H-1,2,4-triazino[5,6-b]indole has been reported to selectively inhibit the replication of BVDV and other pestiviruses (Baginski SG et al., Proc Natl Acad Sci U S A. 2000 Jul 5;97(14):7981-6). There is no treatment strategy available for controlling infections caused by pestiviruses.

Coxsackie viruses belong to the group of the enteroviruses, family of the Picornaviridae. They cause a heterogeneous group of infections including herpangina, aseptic meningitis, a common-cold-like syndrome, a non-paralytic poliomyelitis-like syndrome, epidemic pleurodynia (an acute, febrile, infectious disease generally occurring in epidemics), hand-foot-mouth syndrome, pediatric and adult pancreatitis and serious myocarditis.

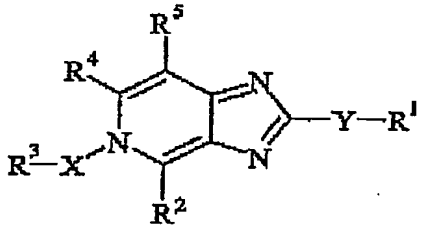
Currently only pleconaril (3-13,5-dimethyl-4-[[3-methyl-5-isoxazolyl)propyl]phenyl]-5-(trifluoromethyl-1,2,4-oxadiazole) and enviroxime [2-amino-1-(isopropylsulfonyl)-6-benzimidazole phenyl ketone oxime] have been studied clinically for the treatment of infections with enteroviruses. Pleconaril is a so called "capsid function-inhibitor"; enviroxime prevents the formation of the RNA replicative intermediate. Enviroxime resulted in only modest clinical and virological benefit in some studies (Phillpotts RJ, Wallace J, Tyrrell DA, Tagart VB. Antimicrob Agents Chemother. 1983 May;23(5):671-5.) and no benefits in others (Miller FD, et al., Chemother. 1985 Jan;27(1):102-6.). Clinical response with pleconaril has been observed in some studies (Rotbart HA, Webster AD. Clin Infect Dis. 2001 Jan 15;32(2):228-35., Rotbart HA. Antiviral Res. 2002 Feb;53(2):83-98), but the compound has not been approved by the Food and Drug Administration (hearing of March 18th, 2002). The inhibitors of Coxsackievirus replication presented here may be used for the treatment of infections with Picornaviridae.

In view of their important pharmacological value, there is a need for drugs having selective activity against viruses belonging to the family of Flaviviridae to which also belongs the hepatitis C virus, and viruses belonging to the family of Picornavidae.

It is the object of the present invention is to provide a novel class of compounds that are active viral inhibitors. One embodiment of present invention are inhibitors of Flaviviridae, preferably inhibitors of the pestivirus replication specifically inhibiting the replication of BVDV; closely related to hepatitis C virus (HCV) and used as a surrogate virus in drug development for HCV infection (Zitzmann N.et al., Proc. Natl. Acad. Sci. USA, 96, 11878-11882 and Bukhtiyarova,-M et al., Antivir-Chem-Chemother. 2001 Nov; 12(6): 367-73). Another embodiment of present invention is a novel class of compounds that can be used for the treatment of infections with Picornaviridae and preferably are active inhibitors of Coxsackievirus replication.

ILLUSTRATIVE EMBODIMENTS OF THE INVENTION

One embodiment of present invention relates to novel substituted imidazo[4,5-c]pyridine derivatives according to the general formula (I)



I

or a pharmaceutically acceptable acid addition salt thereof and their use in a treatment of viral infection or to manufacture a medicament to treat or prevent viral infection, wherein :

R^1 is selected from hydrogen; phenyl substituted with 0-3 R^6; (benzoannellated) 5 or 6 membered heterocyclic ring containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^6; 1-naphthyl substituted with 0-3 R^6; 2-naphthyl substituted with 0-3

R^6; C_{3-7} cycloalkyl; C_{5-7} cycloalkenyl with the proviso that the double bond cannot be adjacent to a nitrogen.

Y is selected from the group $-(CH_2)_{0-5}-$; O; S; NR^{11}; $-CH(CH_3)-$; $-OCH_2-$; $-CH_2O-$; $-OCH_2-CH_2-$; $-CH_2-CH_2O-$; $-CH_2-O-CH_2-$; $-SCH_2-CH_2-$; $-CH_2-CH_2S-$; $-CH_2-S-CH_2-$; $-NR^{11}-CH_2-CH_2-$; $-CH_2-CH_2-NR^{11}-$; $-CH_2-NR^{11}-CH_2-$; $-C(CH_3)_2-$; (cis or trans) $-CH_2-CH=CH-$; (cis or trans) $-CH=CH-CH_2-$.

R^2, R^4 and R^5 are independently selected from hydrogen; straight or branched C_{1-6} alkoxy; straight or branched C_{1-6} alkyl; F; Cl; Br; I; OH; CN; NO_2; NR^7R^8; OCF_3; CF_3; $C(=O)R^9$; phenyl; phenoxy; benzyl; hydroxymethyl.

X is selected from the group $-CH_2-$; $-CH(CH_3)-$; $-CH_2-CH_2-$; $-CH_2-CH_2-CH_2-$; $-CH_2-CH_2-CH_2-CH_2$; $-OCH_2-CH_2-$; $-SCH_2-CH_2-$; $-NR^{10}-CH_2-CH_2-$; C_{3-7} cycloalkylidene; $-C(CH_3)_2-$; $-CH_2-CH(CH_3)-CH_2-$; $-CH(CH_3)-CH_2-CH_2-$; $-CH_2-CH_2-CH(CH_3)-$; $-CH=CH-CH_2-$.

R^3 is selected from phenyl substituted with 0-3 R^{17}; (benzoannellated) 5 or 6 membered heterocyclic ring containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^{17}; 1-naphthyl substituted with 0-3 R^{17}; 2-naphthyl substituted with 0-3 R^{17}; C_{3-7} cycloalkyl; C_{5-7} cycloalkenyl with the proviso that the double bond cannot be adjacent to a nitrogen.

R^6 and R^{17} are independently selected from the group H; straight or branched C_{1-6} alkoxy; straight or branched C_{1-6} alkyl; F; Cl; Br; I; OH; CN; NO_2; $NR^{13}R^{14}$; OCF_3; CF_3; $C(=O)R^{18}$; phenyl; phenoxy; benzyl; hydroxymethyl.

R^7 and R^8 are independently selected from H; straight or branched C_{1-6} alkyl; phenyl; $C(=O)R^{12}$.

alternatively, R^7 and R^8, together with the nitrogen to which they are attached, combine to form a 5-6 membered ring containing 0-1 O or N atoms.

R^9 and R^{18} are independently selected from H; OH; straight or branched C_{1-6} alkyl; straight or branched C_{1-6} alkoxy; $NR^{15}R^{16}$; phenyl.

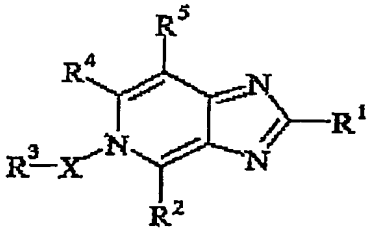
R^{10} and R^{11} are independently selected from the group H; C_{1-6} straight or branched alkyl; phenyl.

R^{12} is selected from the group H; C_{1-6} straight or branched alkyl; phenyl.

R^{13} and R^{14} are independently selected from H; straight or branched C_{1-6} alkyl; phenyl; $C(=O)R^{12}$.

R^{15} and R^{16} are independently selected from the group H; C_{1-6} straight or branched alkyl; phenyl.

A second embodiment of present invention comprises a group of compounds related to the general Formula (I) wherein R^1 is directly linked to the imidazo[4,5-c]pyridine ring structure: Formula (II):



II

or a pharmaceutically acceptable acid addition salt thereof and the use of said compounds in a treatment of viral infection or to manufacture a medicament to treat viral infection, wherein:

R^1 is selected from phenyl substituted with 0-3 R^6; (benzoannellated) 5 or 6 membered heterocyclic ring containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^6; 1-naphthyl substituted with 0-3 R^6; 2-naphthyl substituted with 0-3 R^6; C_{3-7} cycloalkyl; C_{5-7} cycloalkenyl.

R^2, R^4 and R^5 are independently selected from hydrogen; straight or branched C_{1-6} alkoxy; straight or branched C_{1-6} alkyl; F; Cl; Br; I; OH; CN; NO_2; NR^7R^8; OCF_3; CF_3; $C(=O)R^9$; phenyl; phenoxy; benzyl; hydroxymethyl.

X is selected from the group $-CH_2-$; $-CH(CH_3)-$; $-CH_2-CH_2-$; $-CH_2-CH_2-CH_2-$; $-CH_2-CH_2-CH_2-CH_2$; $-OCH_2-CH_2-$; $-SCH_2-CH_2-$; $-NR^{10}-CH_2-CH_2-$; C_{3-7} cycloalkylidene; $-C(CH_3)_2-$; $-CH_2-CH(CH_3)-CH_2-$; $-CH(CH_3)-CH_2-CH_2-$; $-CH_2-CH_2-CH(CH_3)-$; $-CH=CH-CH_2-$.

R^3 is selected from phenyl substituted with 0-3 R^{17}; (benzoannellated) 5 or 6 membered aromatic heterocyclic ring containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^{17}; 1-naphthyl substituted with 0-3 R^{17}; 2-naphthyl substituted with 0-3 R^{17}; C_{3-7} cycloalkyl; C_{5-7} cycloalkenyl with the proviso that the double bond cannot be adjacent to a nitrogen.

R^6 and R^{17} are independently selected from the group H; straight or branched C_{1-6} alkoxy; straight or branched C_{1-6} alkyl; F; Cl; Br; I; OH; CN; NO_2; $NR^{13}R^{14}$; OCF_3; CF_3; $C(=O)R^{18}$; phenyl; phenoxy; benzyl; hydroxymethyl.

R^7 and R^8 are independently selected from H; straight or branched C_{1-6} alkyl; phenyl; $C(=O)R^{12}$.

alternatively, R^7 and R^8, together with the nitrogen to which they are attached, combine to form a 5-6 membered ring containing 0-1 O or N atoms.

R^9 and R^{18} are independently selected from H; OH; straight or branched C_{1-6} alkyl; straight or branched C_{1-6} alkoxy; $NR^{15}R^{16}$; phenyl.

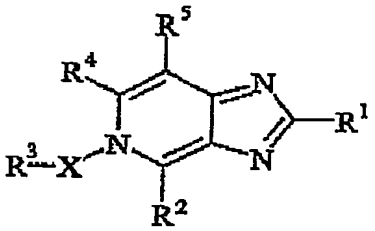
R^{10} is selected from the group H; C_{1-6} straight or branched alkyl; phenyl.

R^{12} is selected from the group H; C_{1-6} straight or branched alkyl; phenyl.

R^{13} and R^{14} are independently selected from H; straight or branched C_{1-6} alkyl; phenyl; $C(=O)R^{12}$.

R^{15} and R^{16} are independently selected from the group H; C_{1-6} straight or branched alkyl; phenyl.

Preferably the second embodiment of present invention comprises the group of compounds according to formula II



II

or a pharmaceutically acceptable acid addition salt thereof and the use of said compounds in a treatment of viral infection or to manufacture a medicament to treat viral infection, wherein:

R^1 is selected from phenyl substituted with 0-3 R^6; (benzoannellated) 5 or 6 membered heterocyclic ring containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^6; 1-naphthyl substituted with 0-3 R^6; 2-naphthyl substituted with 0-3 R^6; C_{3-7} cycloalkyl; C_{5-7} cycloalkenyl.

R^2, R^4 and R^5 are independently selected from hydrogen; straight or branched C_{1-6} alkoxy; straight or branched C_{1-6} alkyl; F; Cl; Br; I; OH; CN; NO_2; NR^7R^8; OCF_3; CF_3; $C(=O)R^9$; phenyl; phenoxy; benzyl; hydroxymethyl.

X is selected from the group $-CH_2-$; $-CH(CH_3)-$; $-CH_2-CH_2-CH_2-$; $-OCH_2-CH_2-$; $-CH=CH-CH_2-$.

R^3 is selected from phenyl substituted with 0-3 R^{17}; (benzoannellated) 5 or 6 membered aromatic heterocyclic ring containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^{17}; 1-naphthyl substituted with 0-3 R^{17}; 2-naphthyl substituted with 0-3

R^{17}; C_{3-7} cycloalkyl; C_{5-7} cycloalkenyl with the proviso that the double bond cannot be adjacent to a nitrogen.

R^6 and R^{17} are independently selected from the group H; straight or branched C_{1-6} alkoxy; straight or branched C_{1-6} alkyl; F; Cl; Br; I; OH; CN; NO_2; $NR^{13}R^{14}$; OCF_3; CF_3; $C(=O)R^{18}$; phenyl; phenoxy; benzyl; hydroxymethyl.

R^7 and R^8 are independently selected from H; straight or branched C_{1-6} alkyl; phenyl; $C(=O)R^{12}$.

alternatively, R^7 and R^8, together with the nitrogen to which they are attached, combine to form a 5-6 membered ring containing 0-1 O or N atoms.

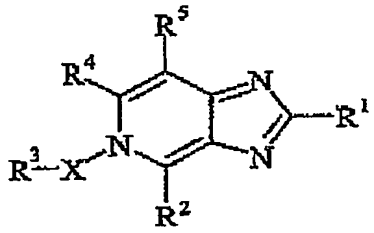
R^9 and R^{18} are independently selected from H; OH; straight or branched C_{1-6} alkyl; straight or branched C_{1-6} alkoxy; $NR^{15}R^{16}$; phenyl.

R^{12} is selected from the group H; C_{1-6} straight or branched alkyl; phenyl.

R^{13} and R^{14} are independently selected from H; straight or branched C_{1-6} alkyl; phenyl; $C(=O)R^{12}$.

R^{15} and R^{16} are independently selected from the group H; C_{1-6} straight or branched alkyl; phenyl.

A more preferred second embodiment of present invention comprises the group of compounds according to formula II



II

or a pharmaceutically acceptable acid addition salt thereof and the use of said compound in a treatment of viral infection or to manufacture a medicament to treat viral infection, wherein:

R^1 is selected from phenyl substituted with 0-3 R^6; (benzoannellated) 5 or 6 membered heterocyclic ring containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^6; 1-naphthyl substituted with 0-3 R^6; 2-naphthyl substituted with 0-3 R^6; C_{3-7} cycloalkyl; C_{5-7} cycloalkenyl.

R^2, R^4 and R^5 are hydrogen.

X is selected from the group $-CH_2-$; $-CH(CH_3)-$; $-CH_2-CH_2-CH_2-$; $-OCH_2-CH_2-$; $-CH=CH-CH_2-$.

R^3 is selected from phenyl substituted with 0-3 R^{17}; (benzoannellated) 5 or 6 membered aromatic heterocyclic ring containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^{17}; 1-naphthyl substituted with 0-3 R^{17}; 2-naphthyl substituted with 0-3 R^{17}; C_{3-7} cycloalkyl; C_{5-7} cycloalkenyl with the proviso that the double bond cannot be adjacent to a nitrogen.

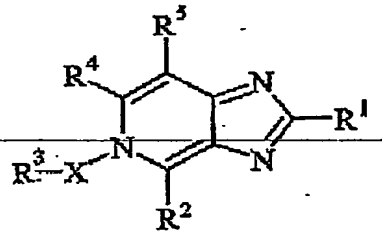
R^6 and R^{17} are independently selected from the group H; straight or branched C_{1-6} alkoxy; straight or branched C_{1-6} alkyl; F; Cl; Br; I; OH; CN; NO_2; $NR^{13}R^{14}$; OCF_3; CF_3; $C(=O)R^9$; phenyl; phenoxy; benzyl; hydroxymethyl.

R^9 is selected from H; OH; straight or branched C_{1-6} alkyl; straight or branched C_{1-6} alkoxy; $NR^{15}R^{16}$; phenyl.

R^{13} and R^{14} are independently selected from H; straight or branched C_{1-6} alkyl; phenyl; $C(=O)R^{12}$.

R^{15} and R^{16} are independendly selected from the group H; C_{1-6} straight or branched alkyl; phenyl.

Yet a more preferred second embodiment of present invention comprises the group of compounds according to formula II



II

or a pharmaceutically acceptable acid addition salt thereof and the use of said compound in a treatment of viral infection or to manufacture a medicament to treat viral infection, wherein:

R^1 is selected from phenyl substituted with 0-3 R^6; (benzoannellated) 5 or 6 membered heterocyclic ring containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^6; 1-naphthyl substituted with 0-3 R^6; 2-naphthyl substituted with 0-3 R^6.

R^2, R^4 and R^5 are hydrogen.

X is selected from $-CH_2-$; $-CH(CH_3)-$; $-CH_2-CH_2-CH_2-$; $-OCH_2-CH_2-$; $-CH=CH-CH_2-$.

R^3 is selected from phenyl substituted with 0-3 R^{17}; (benzoannellated) 5 or 6 membered aromatic heterocyclic ring containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^{17}; 1-naphthyl substituted with 0-3 R^{17}; 2-naphthyl substituted with 0-3 R^{17}.

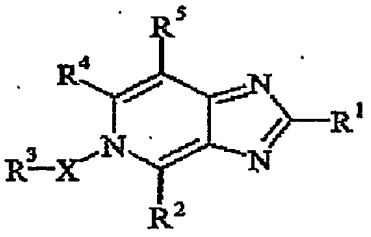
R^6 and R^{17} are independently selected from the group H; straight or branched C_{1-6} alkoxy; straight or branched C_{1-6} alkyl; F; Cl; Br; I; OH; CN; NO_2; $NR^{13}R^{14}$; OCF_3; CF_3; $C(=O)R^9$; phenyl; phenoxy; benzyl; hydroxymethyl.

R^9 is selected from H; OH; straight or branched C_{1-6} alkyl; straight or branched C_{1-6} alkoxy; $NR^{15}R^{16}$; phenyl.

R^{13} and R^{14} are independently selected from H; straight or branched C_{1-6} alkyl; phenyl; $C(=O)R^{12}$.

R^{15} and R^{16} are independently selected from the group H; C_{1-6} straight or branched alkyl; phenyl.

Most preferably the second embodiment of present invention comprises the group of compounds according to formula II



II

or a pharmaceutically acceptable acid addition salt thereof and the use of said compound in a treatment of viral infection or to manufacture a medicament to treat viral infection, wherein

R^1 is selected from phenyl substituted with 0-3 R^6; 5 or 6 membered heterocyclic ring containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^6; 1-naphthyl substituted with 0-3 R^6; 2-naphthyl substituted with 0-3 R^6.

R^2, R^4 and R^5 are hydrogen.

X is selected from $-CH_2-$; $-CH(CH_3)-$; $-CH_2-CH_2-CH_2-$; $-OCH_2-CH_2-$; $-CH=CH-CH_2-$.

R^3 is selected from phenyl substituted with 0-3 R^{17}; 5 or 6 membered aromatic heterocyclic ring containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^{17}; 1-naphthyl substituted with 0-3 R^{17}; 2-naphthyl substituted with 0-3 R^{17}.

R^6 and R^{17} are independently selected from hydrogen; straight or branched C_{1-6} alkoxy; straight or branched C_{1-6} alkyl; F; Cl; Br; I; OH; CN; NO_2; $NR^{13}R^{14}$; OCF_3; CF_3; $C(=O)R^9$; phenyl; phenoxy; benzyl; hydroxymethyl.

R^9 is selected from H; OH; straight or branched C_{1-6} alkyl; straight or branched C_{1-6} alkoxy; $NR^{15}R^{16}$; phenyl.

R^{13} and R^{14} are independently selected from H; straight or branched C_{1-6} alkyl; phenyl; $C(=O)R^{12}$.

R^{15} and R^{16} are independently selected from the group H; C_{1-6} straight or branched alkyl; phenyl.

A third embodiment of present invention is a compound selected from the following group of compounds and its use in a treatment of viral infection or their use to manufacture a medicament to treat a viral infection:

5-(2,6-Difluorobenzyl)-2-(2,6-difluorophenyl)-5*H*-imidazo[4,5-c]pyridine.;
5-Benzyl-2-(2,6-difluorophenyl)-5*H*-imidazo[4,5-c]pyridine;
5-(2,6-Difluorobenzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine;
5-Benzyl-2-phenyl-5*H*-imidazo[4,5-c]pyridine;
2-(2,6-Difluorophenyl)-5-phenethyl-5*H*-imidazo[4,5-c]pyridine.;
2-Phenyl-5-(3-phenyl-propyl)-5*H*-imidazo[4,5-c]pyridine;
5-(2-Chlorobenzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine;
5-(3-Chlorobenzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine;
5-(4-Chlorobenzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine;
5-(2-Methoxybenzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine;
5-(3-Methoxybenzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine;
5-(4-Methoxybenzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine;
5-(4-Methylbenzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine;
5-(3-Fluorobenzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine;
5-(4-Fluorobenzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine;
5-(4-Bromobenzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine;

4-(2-Phenyl-5*H*-imidazo[4,5-c]pyridin-5-ylmethyl)-benzonitrile;
5-(4-Trifluoromethyl-benzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine;
5-(4-Chlorobenzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine hydrochloride;
5-(5-Chloro-2-thienylmethyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine;
5-(2-Naphthylmethyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine;
2-Phenyl-5-(4-phenyl-butyl)-5*H*-imidazo[4,5-c]pyridine;
2-Phenyl-5-(4-phenyl-benzyl)-5*H*-imidazo[4,5-c]pyridine;
(R/S)-2-Phenyl-5-(1-phenyl-ethyl)-5*H*-imidazo[4,5-c]pyridine;
5-(1-Naphthylmethyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine;
5-(2,4-Difluorobenzyl)-2-(2,6-difluorophenyl)-5*H*-imidazo[4,5-c]pyridine;
5-(4-Bromobenzyl)-2-(2-chlorophenyl)-5*H*-imidazo[4,5-c]pyridine;
5-(4-Bromobenzyl)-2-(3-chlorophenyl)-5*H*-imidazo[4,5-c]pyridine;
5-(4-Bromobenzyl)-2-(4-chlorophenyl)-5*H*-imidazo[4,5-c]pyridine;
5-(4-Bromobenzyl)-2-(2-pyridyl)-5*H*-imidazo[4,5-c]pyridine;
5-(4-Bromobenzyl)-2-(2-thienyl)-5*H*-imidazo[4,5-c]pyridine;
5-(4-Bromobenzyl)-2-(1-naphthyl)-5*H*-imidazo[4,5-c]pyridine;
5-(4-Bromobenzyl)-2-(2-naphthyl)-5*H*-imidazo[4,5-c]pyridine;
5-(4-Iodobenzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine;
5-(4-Bromobenzyl)-2-(3-fluorophenyl)-5*H*-imidazo[4,5-c]pyridine;
5-(4-Bromobenzyl)-2-(3-methylphenyl)-5*H*-imidazo[4,5-c]pyridine;
5-(4-Bromobenzyl)-2-(3-bromophenyl)-5*H*-imidazo[4,5-c]pyridine;
5-(4-Bromobenzyl)-2-(3-methoxyphenyl)-5*H*-imidazo[4,5-c]pyridine;
5-(4-Chlorobenzyl)-2-(3-bromophenyl)-5*H*-imidazo[4,5-c]pyridine;
5-(4-Chlorobenzyl)-2-(3-chlorophenyl)-5*H*-imidazo[4,5-c]pyridine;
5-(2-Phenoxy-ethyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine;
5-(3-Phenyl-prop-2-en-1-yl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine and
5-(4-Iodobenzyl)-2-(3-bromophenyl)-5*H*-imidazo[4,5-c]pyridine.

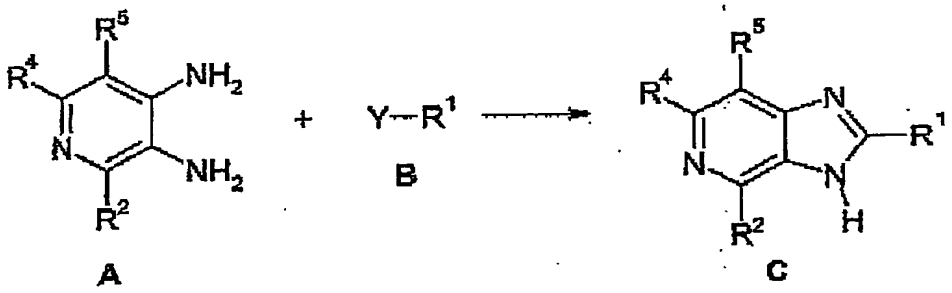
DESCRIPTION OF THE INVENTION

GENERAL METHODS

CHEMISTRY

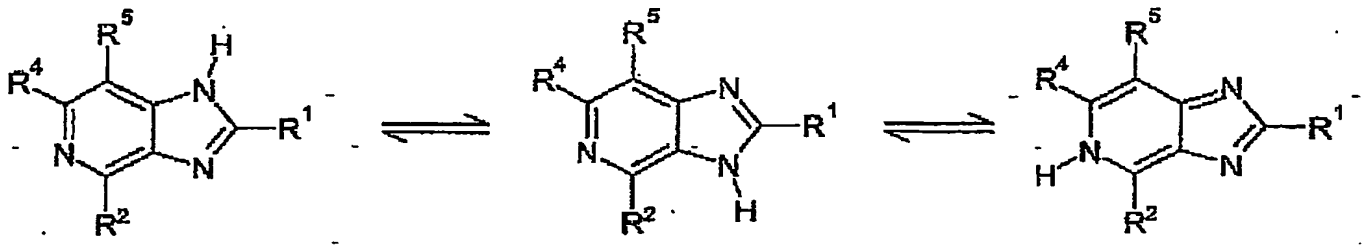
The compounds according to the invention are conveniently prepared in two general steps. First, a (substituted) 3,4-diaminopyridine (A) is reacted with B to give imidazo[4,5-c]pyridines C (scheme 1). If Y is COOH, then the cyclization is carried out under acidic catalysis (preferably in polyphosphoric acid at a temperature between 90 and 200 °C); other methods include reaction in 4N hydrochloric acid at reflux temperature or neat at a temperature between 90 and 180 °C (for aliphatic carboxylic acids). In the case of acid-sensitive groups like alkoxy or thiophene, the reaction can be carried out in phosphorus oxychloride at a temperature between 70 and 120 °C. Alternatively, reaction with aldehydes (Y = CHO) or their bisulfite adducts under oxidative conditions (nitrobenzene, DDQ, copper(II)acetate, O_2, sulfur etc.) gives imidazo[4,5-c]pyridines C. Other methods are the reaction of (substituted) 3,4-diaminopyridines (A) with orthoesters ($Y = C(OR)_3$), anhydrides ($Y = OCOOR$) or acid halogenides ($Y = COX$), etc.

Scheme 1:



The imidazo[4,5-c]pyridines C can be formulated in three tautomeric forms (1*H*, 3*H* or 5*H*), as shown in scheme 2.

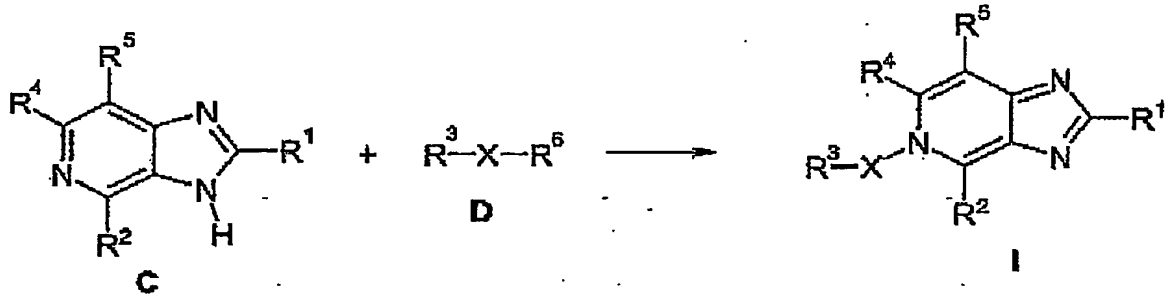
Scheme 2:



1*H*-C 3*H*-C 5*H*-C

Substituents (R^2, R^4 and/or $R^5 \neq H$) can be introduced by two ways: i) either by cylization of an appropiately substituted 3,4-diaminopyridine A or ii) by introduction of the substituent(s) onto the imidazo[4,5-c]pyridine C. For example, halogens can be introduced in position 7 of the imidazo[4,5-c]pyridine C by direct halogenation (R^5 = Br: with bromine in acetic acid or with NBS in acetic acid; R^5 = Cl: with chlorine in acetic acid or with NCS in acetic acid). Another example is the direct nitration ($R^5 = NO_2$), followed by reduction to give the amino group ($R^5 = NH_2$). Substituents in position 4 of the imidazo[4,5-c]pyridine C can be introduced, for example, *via* the corresponding imidazo[4,5-c]pyridine N^5-oxides.

The second and final step is the reaction of the imidazo[4,5-c]pyridines C with an alkylating agent D (R^6 = Cl, Br, etc.) in an appropiate solvent (preferably DMF) under addition of a base (preferably aqueous sodium hydroxide) at ambient temperature (scheme 3).



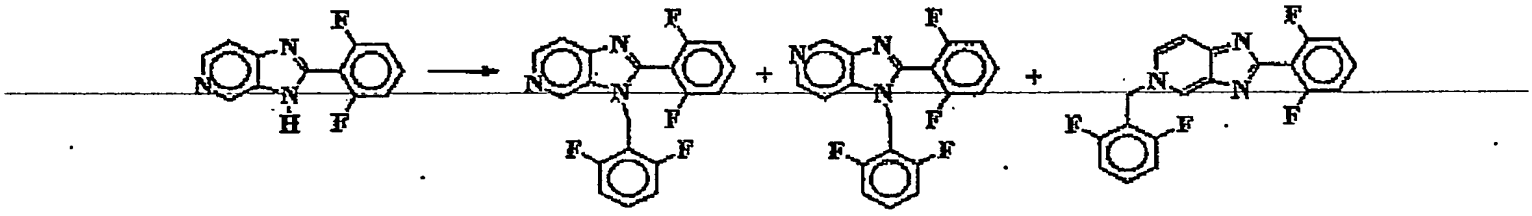
C D I

SCHEME 3:

This reaction gives mixtures of three products (alkylation at the N^1, N^3 or N^5 of the imidazo[4,5-c]pyridine C, respectively). For example, reaction of imidazo[4,5-c]pyridine C

(R^1 = 2,6-difluorophenyl, R^2 = R^4 = R^5 = H) with 2,6-difluorobenzyl bromide gave the following mixture (scheme 4):

SCHEME 4:



16 % 14 % GPRTI-8 (65 %)

This mixture can be separated by column chromatography (silica gel, eluent: mixture of dichloromethane and methanol). The structures of the isolated components can then be assigned by NMR spectroscopy (for example by one-dimensional NOE-techniques: irradiation at the CH_2 resonance frequency; applying this to GPRTI-8 gives signal enhancements of the protons in positions 4 and 6 of the imidazo[4,5-c]pyridine ringsystem) or by single crystal x-ray analysis.

Alternatively, the crude reaction mixture can be recrystallized from an appropiate solvent (mixture), e.g. from a mixture of diisopropyl ether and ethyl acetate, to give the pure N^5 alkylated products.

METHODOLOGY FOR DETERMINATION OF ANTIVIRAL AND CYTOSTATIC ACTIVITY

Antiviral and cytostatic activity are determined by the Methodology described below:

Cells and viruses: Madin-Darbey Bovine Kidney (MDBK) cells were maintained in Dulbecco's modified Eagle medium (DMEM) supplemented with BVDV-free 5% fetal calf serum (DMEME-FCS) at 37°C in a humidified, 5% CO_2 atmosphere. BVDV-1 (strain PE515) was used to assess the antiviral activity in MDBK cells. Vero cells were maintained in the same way as MDBK cells. Vero cells were infected with Coxsackie B3 virus (strain Nancy).

Anti-BVDV assay: Ninety-six-well cell culture plates were seeded with MDBK cells in DMEM-FCS so that cells reached 24 hr later confluency. Then medium was removed and serial 5-fold dilutions of the test compounds were added in a total volume of 100 ul, after which the virus inoculum (100 ul) was added to each well. The virus inoculum used resulted in a greater than 90% destruction of the cell monolayer after 5 days incubation at 37°C. Uninfected cells and cells receiving virus without compound were included in each asay plate. After 5 days, medium was removed and 90 µl of DMEM-FCS and 10 ul of MTS/PMS solution (Promega) was added to each well. Following a 2 hr incubation period at 37°C the optical density of the wells was read at 498 nm in a microplate reader. The 50% effective concentration (EC_{50}) value was defined as the concentration of compound that protects 50% of the cell monolayer from virus-induced cytopathic effect.

EXAMPLES

The following examples illustrate the present invention without being limited thereto. Part A represent the preparation of the compounds whereas Part B represents the pharmacological examples.

PART A

Example 1

Preparation Of 2-(2,6-Difluorophenyl)-1(3)*H*-imidazo[4,5-c]pyridine

A mixture of the 3,4-diaminopyridine (2.00 g), 2,6-difluorobenzoic acid (1 equivalent) and polyphosphoric acid (50 g) was heated at 180°C for 4 h with stirring. Then the mixture was cooled to ambient temperature and poured into ice/water. The resulting mixture was neutralized by addition of solid Na_2CO_3. The crude product was collected by filtration, washed with water and dried. It was used in the next step without further purification.

Recrystallized from water; brownish crystals; mp: 189-190°C; yield: 60%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 13.20 (br s, 1H, NH), 9.04 (br s, 1H, H4), 8.37 (br d, 1H, H6, J=5.4 Hz), 7.76-7.61 (m, 2H, H7/4'), 7.42-7.30 (m, 2H, H3'/5').

Example 2

Preparation Of 2-Phenyl-1(3)*H*-imidazo[4,5-c]pyridine (GPJN-10)

A mixture of the 3,4-diaminopyridine (2.00 g), benzoic acid (1 equivalent) and polyphosphoric acid (50 g) was heated at 190°C for 3 h with stirring. Then the mixture was cooled to ambient temperature and poured into ice/water. The resulting mixture was neutralized by addition of solid Na_2CO_3. The crude product was collected by filtration, washed with water and dried. It was used in the next step without further purification.

Recrystallized from water; off-white crystals; mp: 229-230°C; yield: 96%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.95 (d, 1H, H4, J=1.0 Hz), 8.31 (d, 1H, H6, J=5.4 Hz), 8.28-8.17 (m, 2H, arom. H), 7.64-7.50 (m, 4H, arom. H).

Example 3

Preparation Of 5-(2,6-Difluorobenzyl)-2-(2,6-difluorophenyl)-5*H*-imidazo[4,5-c]pyridine (GPRTI-8)

2-(2,6-Difluorophenyl)-1(3)*H*-imidazo[4,5-c]pyridine (0.500 g) was dissolved in dry DMF (5 mL) and the resulting solution was cooled to 0°C. Aqueous 50% sodium hydroxide (1.5 equivalents) was added and the mixture was stirred for 15 min. Then 2,6-difluorobenzyl bromide (1.2 equivalents) was added portionwise and the resulting mixture was stirred for 24 h at room temperature. Finally, water (50 mL) was added, the precipitate was collected by filtration and dried to give the crude product mixture.

Recrystallized from ethyl acetate; colorless crystals; mp: 195-197°C; yield: 65%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.08 (br s, 1H, H4), 8.09 (dd, 1H, H6, J=6.6, 1.7 Hz), 7.82 (d, 1H, H7, J=6.6 Hz), 7.63-7.46 (m, 2H, H4'/4"), 7.29-7.13 (m, 4H, H3'/5'/3"/5"), 5.87 (s, 2H, CH_2); MS (EI, 70 eV) m/z 357 (M^+, 77%), 338 (4%), 230 (11%), 127 (100%); Anal. ($C_{19}H_{11}F_4N_3$) calcd.: C 63.87%, H 3.10%, N 11.76%, found: C 63.83%, H 3.15%, N 11.63%.

Example 4

Preparation Of 5-Benzyl-2-(2,6-difluorophenyl)-5*H*-imidazo[4,5-c]pyridine (GPJN-1)

Prepared as described in example 3 from 2-(2,6-difluorophenyl)-1(3)*H*-imidazo[4,5-c]pyridine (0.500 g) and benzyl bromide (0.444 g, 1.2 equivalents).

Recrystallized from a mixture of diisopropyl ether and ethyl acetate; off-white crystals; mp: 180-181°C (degr.); yield: 30%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.24 (br d, 1H, H4, J=1.5 Hz), 8.25 (dd, 1H, H6, J=6.9, 1.5 Hz), 7.81 (d, 1H, H7, J=6.9 Hz), 7.60-7.33 (m, 6H, H4'/2"/3"/4"/5"/6"), 7.26-7.13 (m, 2H, H3'/5'), 5.71 (s, 2H, CH_2).

Example 5

Preparation Of 5-(2,6-Difluorobenzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine (GPJN-3)

Prepared as described in example 3 from 2-phenyl-1(3)*H*-imidazo[4,5-c]pyridine (0.500 g) and 2,6-difluorobenzyl bromide (0.636 g, 1.2 equivalents).

Recrystallized from a mixture of diisopropyl ether (25 mL) and ethyl acetate (60 mL); colorless crystals; mp: 214-216°C; yield: 64%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.91 (br s, 1H, H4), 8.39-8.32 (m, 2H, arom. H), 8.01 (dd, 1H, H6, J=6.9, 1.5 Hz), 7.72 (d, 1H, H7, J=6.9 Hz), 7.63-7.37 (m, 4H, arom. H), 7.30-7.16 (m, 2H, H3'/5'), 5.81 (s, 2H, CH_2).

Example 6

Preparation Of 5-Benzyl-2-phenyl-5*H*-imidazo[4,5-c]pyridine (GPJN-4)

Prepared as described in example 3 from 2-phenyl-1(3)*H*-imidazo[4,5-c]pyridine (0.500 g) and benzyl bromide (0.526 g, 1.2 equivalents).

Recrystallized from a mixture of diisopropyl ether (25 mL), ethyl acetate (50 mL) and methanol (4 mL); colorless crystals; mp: 214-216°C; yield: 33%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.09 (d, 1H, H4, J=1.4 Hz), 8.40-8.33 (m, 2H, arom. H), 8.18 (dd, 1H, H6, J=6.9, 1.4 Hz), 7.73 (d, 1H, H7, J=6.9 Hz), 7.52-7.32 (m, 8H, arom. H), 5.66 (s, 2H, CH_2).

Example 7

Preparation Of 2-(2,6-Difluorophenyl)-5-phenethyl-5*H*-imidazo[4,5-c]pyridine (GPJN-2)

Prepared as described in example 3 from 2-(2,6-difluorophenyl)-1(3)*H*-imidazo[4,5-c]pyridine (0.500 g) and 2-phenylethyl bromide (0.480 g, 1.2 equivalents).

Recrystallized from a mixture of diisopropyl ether (50 mL) and ethyl acetate (40 mL); off-white crystals; mp: 184-186°C (degr.); yield: 14%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.02 (br d, 1H, H4, J=1.4 Hz), 8.09 (dd, 1H, H6, J=6.7, 1.4 Hz), 7.74 (d, 1H, H7, J=6.7 Hz), 7.60-7.45 (m, 1H, H4'), 7.34-7.12 (m, 7H, H3'/5'/2''/3''/4''/5''/6''), 4.74 (t, 2H, N-CH_2, J=7.4 Hz), 3.26 (t, 2H, CH_2, J=7.4 Hz).

Example 8

Preparation Of 2-Phenyl-5-(3-phenyl-propyl)-5*H*-imidazo[4,5-c]pyridine (GPJN-14)

Prepared as described in example 3 from 2-phenyl-1(3)*H*-imidazo[4,5-c]pyridine (0.300 g) and 1-bromo-3-phenylpropane (0.367 g, 1.2 equivalents).

Recrystallized from a mixture of diisopropyl ether (10 mL) and ethyl acetate (7 mL); off-white crystals; mp: 44-46°C; yield: 44%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.95 (d, 1H, H4, J=1.4 Hz), 8.40-8.33 (m, 2H, arom. H), 8.09 (dd, 1H, H6, J=6.8, 1.4 Hz), 7.71 (d, 1H, H7, J=6.8 Hz), 7.52-7.13 (m, 8H, arom. H), 4. 84 (t, 2H, N-CH_2, J=7.2 Hz), 2.65-2.57 (m, 2H, CH_2), 2.31-2.16 (m, 2H, CH_2).

Example 9

Preparation Of 5-(2-Chlorobenzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine (GPJN-7)

Prepared as described in example 3 from 2-phenyl-1(3)*H*-imidazo[4,5-c]pyridine (0.300 g) and 2-chlorobenzyl chloride (0.297 g, 1.2 equivalents).

Recrystallized from a mixture of diisopropyl ether (25 mL) and ethyl acetate (65 mL); colorless crystals; mp: 224-225°C; yield: 52%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.99 (d, 1H, H4, J=1.6 Hz), 8.40-8.33 (m, 2H, arom. H), 8.10 (dd, 1H, H6, J=6.7, 1.6 Hz), 7.75 (d, 1H, H7, J=6.7 Hz), 7.59-7.34 (m, 6H, arom. H), 7.18-7.12 (m, 1H, arom. H), 5.80 (s, 2H, CH_2).

Example 10

Preparation Of 5-(3-Chlorobenzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine (GPJN-8)

Prepared as described in example 3 from 2-phenyl-1(3)*H*-imidazo[4,5-c]pyridine (0.300 g) and 3-chlorobenzyl bromide (0.379 g, 1.2 equivalents).

Recrystallized from a mixture of diisopropyl ether (10 mL) and ethyl acetate (27 mL); colorless crystals; mp: 210-212°C; yield: 54%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.12 (d, 1H, H4, J=1.5 Hz), 8.39-8.32 (m, 2H, arom. H), 8.20 (dd, 1H, H6, J=6.7, 1.5 Hz), 7.74 (d, 1H, H7, J=6.7 Hz), 7.61-7.38 (m, 7H, arom. H), 5.66 (s, 2H, CH_2).

Example 11

Preparation Of 5-(4-Chlorobenzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine (GPJN-9)

Prepared as described in example 3 from 2-phenyl-1(3)*H*-imidazo[4,5-c]pyridine (0.300 g) and 4-chlorobenzyl chloride (0.297 g, 1.2 equivalents).

Recrystallized from a mixture of diisopropyl ether (10 mL) and ethyl acetate (24 mL); colorless crystals; mp: 211-212°C; yield: 55%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.09 (d, 1H, H4, J=1.5 Hz), 8.40-8.33 (m, 2H, arom. H), 8.17 (dd, 1H, H6, J=6.9, 1.5 Hz), 7.73 (d, 1H, H7, J=6.9 Hz), 7.52-7.40 (m, 7H, arom. H), 5.66 (s, 2H, CH_2).

Example 12

Preparation Of 5-(2-Methoxybenzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine (GPJN-11)

Prepared as described in example 3 from 2-phenyl-1(3)*H*-imidazo[4,5-c]pyridine (0.300 g) and 2-methoxybenzyl chloride (0.288 g, 1.2 equivalents).

Recrystallized from a mixture of diisopropyl ether (10 mL) and ethyl acetate (30 mL); colorless crystals; mp: 182-184°C; yield: 60%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.94 (d, 1H, H4, J=1.6 Hz), 8.39-8.32 (m, 2H, arom. H), 8.08 (dd, 1H, H6, J=6.7, 1.6 Hz), 7.69 (d, 1H, H7, J=6.7 Hz), 7.51-7.29 (m, 5H, arom. H), 7.10-6.94 (m, 2H, arom. H), 5.61 (s, 2H, CH_2), 3.84 (s, 3H, OCH_3).

Example 13

Preparation Of 5-(3-Methoxybenzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine (GPJN-12)

Prepared as described in example 3 from 2-phenyl-1(3)*H*-imidazo[4,5-c]pyridine (0.300 g) and 3-methoxybenzyl chloride (0.288 g, 1.2 equivalents).

Recrystallized from a mixture of diisopropyl ether (10 mL) and ethyl acetate (23 mL); colorless crystals; mp: 157-158°C; yield: 62%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.10 (d, 1H, H4, J=1.7 Hz), 8.40-8.33 (m, 2H, arom. H), 8.18 (dd, 1H, H6, J=6.7, 1.7 Hz), 7.72 (d, 1H, H7, J=6.7 Hz), 7.52-7.27 (m, 4H, arom. H), 7.10-6.89 (m, 3H, arom. H), 5.61 (s, 2H, CH_2), 3.75 (s, 3H, OCH_3).

Example 14

Preparation Of 5-(4-Methoxybenzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine (GPJN-13)

Prepared as described in example 3 from 2-phenyl-1(3)*H*-imidazo[4,5-c]pyridine (0.300 g) and 4-methoxybenzyl chloride (0.288 g, 1.2 equivalents).

Recrystallized from a mixture of diisopropyl ether (10 mL) and ethyl acetate (31 mL); colorless crystals; mp: 211-212°C; yield: 52%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.07 (d, 1H, H4, J=1.5 Hz), 8.39-8.32 (m, 2H, arom. H), 8.16 (dd, 1H, H6, J=6.9, 1.5 Hz), 7.70 (d, 1H, H7, J=6.9 Hz), 7.51-7.37 (m, 5H, arom. H), 6.99-6.92 (AA'BB', 2H, arom. H), 5.57 (s, 2H, CH_2), 3.73 (s, 3H, OCH_3).

Example 15

Preparation Of 5-(2-Methylbenzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine (GPJN-20)

Prepared as described in example 3 from 2-phenyl-1(3)*H*-imidazo[4,5-c]pyridine (0.300 g) and 2-methylbenzyl chloride (0.259 g, 1.2 equivalents).

Recrystallized from a mixture of diisopropyl ether (10 mL) and ethyl acetate (44 mL); colorless crystals; mp: 223-224°C; yield: 60%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.93 (d, 1H,

H4, J=1.6 Hz), 8.41-8.33 (m, 2H, arom. H), 8.04 (dd, 1H, H6, J=6.7, 1.6 Hz), 7.75 (d, 1H, H7, J=6.7 Hz), 7.53-7.15 (m, 5H, arom. H), 6.92 (br d, 1H, arom. H, J=7.0 Hz); 5.73 (s, 2H, CH_2), 2.32 (s, 3H, CH_3).

Example 16

Preparation Of 5-(3-Methylbenzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine (GPJN-21)

Prepared as described in example 3 from 2-phenyl-1(3)*H*-imidazo[4,5-c]pyridine (0.300 g) and 3-methylbenzyl chloride (0.259 g, 1.2 equivalents).

Recrystallized from a mixture of diisopropyl ether (10 mL) and ethyl acetate (15 mL); colorless crystals; mp: 183-185°C; yield: 46%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.08 (d, 1H, H4, J=1.5 Hz), 8.40-8.33 (m, 2H, arom. H), 8.16 (dd, 1H, H6, J=6.7, 1.5 Hz), 7.72 (d, 1H, H7, J=6.7 Hz), 7.52-7.14 (m, 7H, arom. H), 5.61 (s, 2H, CH_2), 2.29 (s, 3H, CH_3).

Example 17

Preparation Of 5-(4-Methylbenzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine (GPJN-15)

Prepared as described in example 3 from 2-phenyl-1(3)*H*-imidazo[4,5-c]pyridine (0.300 g) and 4-methylbenzyl chloride (0.259 g, 1.2 equivalents).

Recrystallized from a mixture of diisopropyl ether (10 mL) and ethyl acetate (32 mL); colorless crystals; mp: 206-208°C; yield: 57%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.07 (d, 1H, H4, J=1.5 Hz), 8.39-8.32 (m, 2H, arom. H), 8.15 (dd, 1H, H6, J=6.7, 1.5 Hz), 7.71 (d, 1H, H7, J=6.7 Hz), 7.52-7.17 (m, 7H, arom. H), 5.60 (s, 2H, CH_2), 2.28 (s, 3H, CH_3).

Example 18

Preparation Of 5-(2-Fluorobenzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine (GPJN-17)

Prepared as described in example 3 from 2-phenyl-1(3)*H*-imidazo[4,5-c]pyridine (0.300 g) and 2-fluorobenzyl bromide (0.349 g, 1.2 equivalents).

Recrystallized from a mixture of diisopropyl ether (10 mL) and ethyl acetate (37 mL); colorless crystals; mp: 209-211°C; yield: 67%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.01 (br s, 1H, H4), 8.41-8.33 (m, 2H, arom. H), 8.06 (dd, 1H, H6, J=6.8, 1.6 Hz), 7.74 (d, 1H, H7, J=6.8 Hz), 7.52-7.21 (m, 7H, arom. H), 5.76 (s, 2H, CH_2).

Example19

Preparation Of 5-(3-Fluorobenzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine (GPJN-18)

Prepared as described in example 3 from 2-phenyl-1(3)*H*-imidazo[4,5-c]pyridine (0.300 g) and 3-fluorobenzyl bromide (0.349 g, 1.2 equivalents).

Recrystallized from a mixture of diisopropyl ether (10 mL) and ethyl acetate (34 mL); colorless crystals; mp: 228-230°C; yield: 55%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.12 (d, 1H, H4, J=1.5 Hz), 8.41-8.33 (m, 2H, arom. H), 8.20 (dd, 1H, H6, J=6.7, 1.5 Hz), 7.74 (d, 1H, H7, J=6.7 Hz), 7.52-7.15 (m, 7H, arom. H), 5.67 (s, 2H, CH_2).

Example 20

Preparation Of 5-(4-Fluorobenzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine (GPJN-19)

Prepared as described in example 3 from 2-phenyl-1(3)*H*-imidazo[4,5-c]pyridine (0.300 g) and 4-fluorobenzyl chloride (0.267 g, 1.2 equivalents).

Recrystallized from a mixture of diisopropyl ether (10 mL) and ethyl acetate (19 mL); colorless crystals; mp: 205-206°C; yield: 56%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.11 (d, 1H, H4, J=1.7 Hz), 8.40-8.33 (m, 2H, arom. H), 8.18 (dd, 1H, H6, J=6.8, 1.7 Hz), 7.73 (d, 1H, H7, J=6.8 Hz), 7.61-7.37 (m, 5H, arom. H), 7.30-7.18 (m, 2H, arom. H), 5.64 (s, 2H, CH_2).

Example 21

Preparation Of 5-(4-*tert*-Butyl-benzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine (GPJN-16)

Prepared as described in example 3 from 2-phenyl-1(3)*H*-imidazo[4,5-c]pyridine (0.300 g) and 4-*tert*-butylbenzyl bromide (0.419 g, 1.2 equivalents).

Recrystallized from a mixture of diisopropyl ether (10 mL) and ethyl acetate (23 mL); colorless crystals; mp: 213-215°C; yield: 49%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.07 (d, 1H, H4, J=1.6 Hz), 8.39-8.33 (m, 2H, arom. H), 8.17 (dd, 1H, H6, J=6.7, 1.6 Hz), 7.71 (d, 1H, H7, J=6.7 Hz), 7.53-7.35 (m, 7H, arom. H), 5.61 (s, 2H, CH_2), 1.24 (s, 9H, $(CH_3)_3$).

Example 22

Preparation Of 5-(4-Bromobenzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine (GPJN-22)

Prepared as described in example 3 from 2-phenyl-1(3)*H*-imidazo[4,5-c]pyridine (0.300 g) and 4-bromobenzyl bromide (0.461 g, 1.2 equivalents).

Recrystallized from a mixture of diisopropyl ether (10 mL) and ethyl acetate (26 mL); colorless crystals; mp: 212-214°C; yield: 45%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.09 (br s, 1H, H4), 8.40-8.33 (m, 2H, arom. H), 8.17 (dd, 1H, H6, J=6.8, 1.5 Hz), 7.73 (d, 1H, H7, J=6.8 Hz), 7.64-7.58 (AA'BB', 2H, arom. H), 7.52-7.37 (m, 5H, arom. H), 5.64 (s, 2H, CH_2).

Example23

Preparation Of 4-(2-Phenyl-5*H*-imidazo[4,5-c]pyridin-5-ylmethyl)-benzonitrile (GPJN-23)

Prepared as described in example 3 from 2-phenyl-1(3)*H*-imidazo[4,5-c]pyridine (0.300 g) and 4-bromomethyl-benzonitrile (0.362 g, 1.2 equivalents).

Recrystallized twice from a mixture of diisopropyl ether (10 mL) and ethyl acetate (25 mL); pale orange crystals; mp: 93°C (degr.); yield: 34%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.10 (d, 1H, H4, J=1.5 Hz), 8.40-8.33 (m, 2H, arom. H), 8.18 (dd, 1H, H6, J=6.9, 1.5 Hz), 7.91-7.85 (AA'BB', 2H, arom. H), 7.75 (d, 1H, H7, J=6.9 Hz), 7.61-7.55 (AA'BB', 2H, arom. H), 7.52-7.37 (m, 3H, arom. H), 5.77 (s, 2H, CH_2).

Example 24

Preparation Of 5-(4-Trifluoromethyl-benzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine (GPJN-24)

Prepared as described in example 3 from 2-phenyl-1(3)*H*-imidazo[4,5-c]pyridine (0.300 g) and 4-trifluoromethylbenzyl bromide (0.441 g, 1.2 equivalents).

Recrystallized from a mixture of diisopropyl ether (10 mL) and ethyl acetate (20 mL); colorless crystals; mp: 230-232°C; yield: 50%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.12 (d, 1H, H4, J=1.6 Hz), 8.40-8.33 (m, 2H, arom. H), 8.19 (dd, 1H, H6, J=6.9, 1.6 Hz), 7.81-7.73 (m, 3H, arom. H), 7.65-7.59 (AA'BB', 2H, arom. H), 7.53-7.38 (m, 3H, arom. H), 5.78 (s, 2H, CH_2).

Example 25

Preparation Of 5-(4-Chlorobenzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine hydrochloride (GPJN-9 x HCl)

98 mg of 5-(4-chloro-benzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine (GPJN-9) were dissolved in dry dichloromethane (18 mL) and to this solution was added one equivalent of HCl (1M in diethyl ether). After 2 hours the precipitate was collected by filtration and dried to give 70 % of the hydrochloride; colorless crystals; mp:147-148°C (degr.).

Example 26

Preparation Of 5-(5-Chloro-2-thienylmethyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine (GPJN-25)

Prepared as described in example 3 from 2-phenyl-1(3)*H*-imidazo[4,5-c]pyridine (0.300 g) and 2-chloro-5-chloromethyl-thiophene (0.308 g, 1.2 equivalents).

Recrystallized from a mixture of diisopropyl ether (20 mL) and ethyl acetate (50 mL); off-white crystals; mp: 215-216°C; yield: 39%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.07 (d, 1H, H4, J=1.5 Hz), 8.40-8.33 (m, 2H, arom. H), 8.19 (dd, 1H, H6, J=6.8, 1.5 Hz), 7.74 (d, 1H, H7, J=6.8 Hz), 7.55-7.37 (m, 3H, arom. H), 7.28 (d, 1H, thiophene-H, J=3.8 Hz), 7.08 (d, 1H, thiophene-H, J=3.8 Hz), 5.81 (s, 2H, CH_2).

Example 27

Preparation Of 5-(2-Naphthylmethyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine (GPJN-26)

Prepared as described in example 3 from 2-phenyl-1(3)*H*-imidazo[4,5-c]pyridine (0.300 g) and 2-bromomethyl-naphthalene (0.408 g, 1.2 equivalents).

Recrystallized from a mixture of ethyl acetate (20 mL) and ethanol (8 mL); colorless crystals; mp: 267°C; yield: 36%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.17 (d, 1H, H4, J=1.7 Hz), 8.40-8.33 (m, 2H, arom. H), 8.23 (dd, 1H, H6, J=6.7, 1.7 Hz), 7.99-7.87 (m, 4H, arom. H), 7.74 (d, 1H, H7, J=6.7 Hz), 7.60-7.37 (m, 6H, arom. H), 5.84 (s, 2H, CH_2).

Example28

Preparation Of 2-Phenyl-5-(4-phenyl-butyl)-5*H*-imidazo[4,5-c]pyridine (GPJN-27)

Prepared as described in example 3 from 2-phenyl-1(3)*H*-imidazo[4,5-c]pyridine (0.300 g) and 1-chloro-4-phenylbutane (0.311 g, 1.2 equivalents).

Recrystallized from a mixture of diisopropyl ether (20 mL) and ethyl acetate (11 mL); colorless crystals; mp: 119-120°C; yield: 53%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.95 (d, 1H, H4, J=1.4 Hz), 8.40-8.33 (m, 2H, arom. H), 8.07 (dd, 1H, H6, J=6.8, 1.4 Hz), 7.70 (d, 1H, H7, J=6.8 Hz), 7.52-7.37 (m, 3H, arom. H), 7.31-7.10 (m, 5H, arom. H), 4.46 (t, 2H, CH_2, J=7.1 Hz), 2.62 (t, 2H, CH_2, J=7.6 Hz), 2.00-1.85 (m, 2H, CH_2), 1.63-1.46 (m, 2H, CH_2).

Example 29

Preparation Of 5-(3-Methyl-but-2-enyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine (GPJN-28)

Prepared as described in example 3 from 2-phenyl-1(3)*H*-imidazo[4,5-c]pyridine (0.300 g) and 4-bromo-2-methylbut-2-ene (0.275 g, 1.2 equivalents).

Recrystallized from a mixture of diisopropyl ether (20 mL) and ethyl acetate (11 mL); off-white crystals; mp: 162-163°C; yield: 58%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.86 (d, 1H, H4, J=1.7 Hz), 8.40-8.33 (m, 2H, arom. H), 7.99 (dd, 1H, H6, J=6.8, 1.7 Hz), 7.71 (d, 1H, H7, J=6.8 Hz), 7.52-7.37 (m, 3H, arom. H), 5.57-5.47 (m, 1H, =CH), 5.06 (br d, 2H, CH_2, J=7.4 Hz), 1.86 (br s, 3H, CH_3), 1.77 (br s, 3H, CH_3).

Example 30

Preparation Of 5-Ethyl-2-phenyl-5*H*-imidazo[4,5-c]pyridine (GPJN-29)

Prepared as described in example 3 from 2-phenyl-1(3)*H*-imidazo[4,5-c]pyridine (0.300 g) and ethyl iodide (0.288 g, 1.2 equivalents).

Recrystallized from a mixture of diisopropyl ether (5 mL) and ethyl acetate (12 mL); colorless crystals; mp: 188°C; yield: 22%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.96 (d, 1H, H4, J=1.6 Hz), 8.40-8.33 (m, 2H, arom. H), 8.09 (dd, 1H, H6, J=6.8, 1.6 Hz), 7.71 (d, 1H, H7, J=6.8 Hz), 7.52-7.36 (m, 3H, arom. H), 4.47 (q, 2H, CH_2, J=7.3 Hz), 1.52 (t, 3H, CH_3, J=7.3 Hz).

Example 31

Preparation Of 5-(2-(Diisopropylamino)ethyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine (GPJN-30)

Prepared as described in example 3 from 2-phenyl-1(3)*H*-imidazo[4,5-c]pyridine (0.300 g), and 2-(diisopropylamino)ethyl chloride hydrochloride (0.369 g, 1.2 equivalents).

Recrystallized from a mixture of diisopropyl ether (20 mL) and ethyl acetate (10 mL); colorless crystals; mp: 151-152°C; yield: 57%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.80 (d, 1H, H4, J=1.5 Hz), 8.39-8.33 (m, 2H, arom. H), 7.99 (dd, 1H, H6, J=6.8, 1.5 Hz), 7.67 (d, 1H, H7, J=6.8 Hz), 7.51-7.36 (m, 3H, arom. H), 4.36 (t, 2H, CH_2, J=5.4 Hz), 3.04-2.84 (m, 4H, 2 x CH and CH_2), 0.78 (d, 12H, 4 x CH_3, J=6.6 Hz).

Example 32

Preparation Of 5-(4-Pyridylmethyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine (GPJN-31)

Prepared as described in example 3 from 2-phenyl-1(3)*H*-imidazo[4,5-c]pyridine (0.300 g), and 4-chloromethyl-pyridine hydrochloride (0.303 g, 1.2 equivalents).

Recrystallized from a mixture of diisopropyl ether (20 mL) and ethyl acetate (15 mL); colorless crystals (hygroscopic); yield: 25%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.09 (d, 1H, H4, J=1.6 Hz), 8.60-8.57 (m, 2H, pyridine-H2/6), 8.40-8.33 (m, 2H, arom. H), 8.17 (dd, 1H, H6, J=6.8, 1.6 Hz), 7.67 (d, 1H, H7, J=6.8 Hz), 7.52-7.37 (m, 3H, arom. H), 7.31-7.28 (m, 2H, pyridine-H3/5), 5.74 (s, 2H, CH_2).

Example 33

Preparation Of 5-(2-Pyridylmethyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine (GPJN-34)

Prepared as described in example 3 from 2-phenyl-1(3)*H*-imidazo[4,5-c]pyridine (0.300 g), and 2-chloromethyl-pyridine hydrochloride (0.303 g, 1.2 equivalents).

Recrystallized from a mixture of diisopropyl ether (20 mL) and ethyl acetate (17 mL); colorless crystals; mp: 102-103°C; yield: 44%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.02 (d, 1H, H4, J=1.4 Hz), 8.53 (ddd, 1H, pyridine-H6, J=4.7, 1.7, 0.8 Hz), 8.40-8.33 (m, 2H, arom. H), 8.13 (dd, 1H, H6, J=6.8, 1.4 Hz), 7.90-7.82 (m, 1H, pyridine-H4), 7.72 (d, 1H, H7, J=6.8 Hz), 7.52-7.33 (m, 5H, arom. H), 5.79 (s, 2H, CH_2).

Example 34

Preparation Of 5-(3-Pyridylmethyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine (GPJN-35)

Prepared as described in example 3 from 2-phenyl-1(3)*H*-imidazo[4,5-c]pyridine (0.300 g), and 3-chloromethyl-pyridine hydrochloride (0.303 g, 1.2 equivalents).

Recrystallized from a mixture of diisopropyl ether (20 mL) and ethyl acetate (41 mL); off-white crystals; mp: 53°C (degr.); yield: 46%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.14 (d, 1H, H4, J=1.6 Hz), 8.76 (br d, 1H, pyridine-H2), 8.57 (dd, 1H, pyridine-H6, J=4.8, 1.6 Hz), 8.40-8.33 (m, 2H, arom. H), 8.22 (dd, 1H, H6, J=6.8, 1.6 Hz), 7.90-7.84 (m, 1H, pyridine-H4), 7.74 (d, 1H, H7, J=6.8 Hz), 7.52-7.38 (m, 45H, arom. H), 5.71 (s, 2H, CH_2).

Example 35

Preparation Of 2-Phenyl-5-(4-phenyl-benzyl)-5*H*-imidazo[4,5-c]pyridine (GPJN-32)

Prepared as described in example 3 from 2-phenyl-1(3)*H*-imidazo[4,5-c]pyridine (0.300 g) and 4-chloromethyl-biphenyl (0.374 g, 1.2 equivalents).

Recrystallized from a mixture of ethyl acetate (50 mL) and ethanol (1.5 mL); colorless crystals; mp: 247-248°C; yield: 65%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.14 (d, 1H, H4,

J=1.4 Hz), 8.40-8.33 (m, 2H, arom. H), 8.22 (dd, 1H, H6, J=6.8, 1.4 Hz), 7.75 (d, 1H, H7, J=6.8 Hz), 7.72-7.30 (m, 12H, arom. H), 5.71 (s, 2H, CH_2).

Example 36

Preparation Of (R/S)-2-Phenyl-5-(1-phenyl-ethyl)-5*H*-imidazo[4,5-c]pyridine (GPJN-33)

Prepared as described in example 3 from 2-phenyl-1(3)*H*-imidazo[4,5-c]pyridine (0.300 g) and (R/S)-1-phenylethyl bromide (0.341 g, 1.2 equivalents).

Recrystallized from a mixture of diisopropyl ether (20 mL) and ethyl acetate (40 mL); colorless crystals; mp: 190-192°C; yield: 57%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.13 (d, 1H, H4, J=1.6 Hz), 8.39-8.33 (m, 2H, arom. H), 8.19 (dd, 1H, H6, J=6.7, 1.6 Hz), 7.70 (d, 1H, H7, J=6.7 Hz), 7.53-7.31 (m, 8H, arom. H), 6.01 (q, 1H, CH, J=7.0 Hz), 2.04 (d, 3H, CH_3, J=7.0 Hz).

Example 37

Preparation Of 5-(1-Naphthylmethyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine (GPJN-36)

Prepared as described in example 3 from 2-phenyl-1(3)*H*-imidazo[4,5-c]pyridine (0.300 g) and 1-chloromethyl-naphthalene (0.326 g, 1.2 equivalents).

Recrystallized from a mixture of diisopropyl ether (10 mL) and ethyl acetate (45 mL); colorless crystals; mp: 191°C; yield: 73%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.08 (d, 1H, H4, J=1.5 Hz), 8.39-8.33 (m, 2H, arom. H), 8.23-8.15 (m, 2H, arom. H), 7.75 (d, 1H, H7, J=6.8 Hz), 7.68-7.37 (m, 6H, arom. H), 7.25 (br d, 1H, arom. H, J=6.6 Hz), 6.22 (s, 2H, CH_2).

Example 38

Preparation Of 5-(Cyclohexylmethyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine (GPJN-37)

Prepared as described in example 3 from 2-phenyl-1(3)*H*-imidazo[4,5-c]pyridine (0.300 g) and cyclohexylmethyl bromide (0.327 g, 1.2 equivalents) with heating at 80°C.

Recrystallized from a mixture of diisopropyl ether (20 mL) and ethyl acetate (14 mL); colorless crystals; mp: 188-189°C; yield: 36%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.89 (d, 1H, H4, J=1.5 Hz), 8.39-8.33 (m, 2H, arom. H), 8.03 (dd, 1H, H6, J=6.6, 1.5 Hz), 7.69 (d, 1H, H7, J=6.6 Hz), 7.52-7.37 (m, 3H, arom. H), 4.28 (d, 2H, CH_2, J=7.4 Hz), 2.02-0.92 (m, 11H, cyclohexyl H).

Example 39

Preparation Of 5-(3-Methyl-1-butyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine (GPJN-38)

Prepared as described in example 3 from 2-phenyl-1(3)*H*-imidazo[4,5-c]pyridine (0.300 g) and 1-bromo-3-methylbutane (0.279 g, 1.2 equivalents).

Recrystallized from a mixture of diisopropyl ether (20 mL) and ethyl acetate (17 mL); colorless crystals; mp: 207°C; yield: 37%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.96 (d, 1H, H4, J=1.5 Hz), 8.40-8.34 (m, 2H, arom. H), 8.09 (dd, 1H, H6, J=6.8, 1.5 Hz), 7.70 (d, 1H, H7, J=6.8 Hz), 7.52-7.37 (m, 3H, arom. H), 4.45 (t, 2H, CH_2, J=7.4 Hz), 1.87-1.75 (m, 2H, CH_2), 1.53 (hept, 1H, CH, J=6.6 Hz), 0.94 (d, 6H, $(CH_3)_2$).

Example 40

Preparation Of 5-(4-Fluorobenzyl)-2-(2,6-difluorophenyl)-5*H*-imidazo[4,5-c]pyridine (GPJN-39)

Prepared as described in example 3 from 2-(2,6-difluorophenyl)-1(3)*H*-imidazo[4,5-c]pyridine (0.300 g) and 4-fluorobenzyl chloride (0.225 g, 1.2 equivalents).

Recrystallized from a mixture of diisopropyl ether (10 mL) and ethyl acetate (10 mL); off-white crystals; mp: 104-105°C; yield: 48%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.26 (d, 1H, H4, J=1.4 Hz), 8.26 (dd, 1H, H6, J=6.8, 1.4 Hz), 7.81 (d, 1H, H7, J=6.8 Hz), 7.61-7.45 (m, 3H, arom. H), 7.30-7.13 (m, 4H, arom. H), 5.69 (s, 2H, CH_2).

Example 41

Preparation Of 5-(2,4-Difluorobenzyl)-2-(2,6-difluorophenyl)-5*H*-imidazo[4,5-c]pyridine (GPJN-40)

Prepared as described in example 3 from 2-(2,6-difluorophenyl)-1(3)*H*-imidazo[4,5-c]pyridine (0.300 g) and 2,4-difluorobenzyl bromide (0.322 g, 1.2 equivalents).

Recrystallized from a mixture of diisopropyl ether (10 mL) and ethyl acetate (8 mL); off-white crystals; mp: 186-188°C; yield: 29%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.16 (br s, 1H, H4), 8.18 (dd, 1H, H6, J=6.8, 1.3 Hz), 7.82 (d, 1H, H7, J=6.8 Hz), 7.64-7.11 (m, 6H, arom. H), 5.78 (s, 2H, CH_2).

Example42

Preparation Of 2-(2,6-Difluorophenyl)- 5-(2,4,6-trifluorobenzyl)-5*H*-imidazo[4,5-c]pyridine (GPJN-41)

Prepared as described in example 3 from 2-(2,6-difluorophenyl)-1(3)*H*-imidazo[4,5-c]pyridine (0.200 g) and 2,4,6-trifluorobenzyl bromide (0.234 g, 1.2 equivalents).

Recrystallized from a mixture of diisopropyl ether (10 mL) and ethyl acetate (8 mL); off-white crystals; mp: 186-187°C; yield: 26%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.06 (br s, 1H, H4), 8.08 (dd, 1H, H6, J=6.8, 1.6 Hz), 7.81 (d, 1H, H7, J=6.8 Hz), 7.61-7.46 (m, 1H, H4'), 7.42-7.13 (m, 4H, H3'/5'/3''/5''), 5.82 (s, 2H, CH_2).

Example 43

Preparation Of 5-(4-Bromobenzyl)-2-ethyl-5*H*-imidazo[4,5-c]pyridine (GPJN-48)

A mixture of the 3,4-diaminopyridine (1.00 g), propionic acid (1 equivalent) and polyphosphoric acid (25 g) was heated at 150°C for 1 h and then at 190°C for 2 h with stirring. Then the mixture was cooled to ambient temperature and poured into ice/water. The resulting mixture was made alkaline by addition of 2N NaOH and extracted with ethyl acetate (100 mL) six times. The combined organic phases were dried (Na_2SO_4) and evaporated to give the crude product, which was recrystallized from ethyl acetate (100 mL) to give 56% of 2-ethyl-1(3)*H*-imidazo[4,5-c]pyridine as a white powder.

2-Ethyl-1(3)*H*-imidazo[4,5-c]pyridine (0.245 g) was dissolved in dry DMF (6 mL) and the resulting solution was cooled to 0°C. Aqueous 33% sodium hydroxide (1.5 equivalents) was

added and the mixture was stirred for 15 min. Then 4-bromobenzyl bromide (1.2 equivalents) was added portionwise and the resulting mixture was stirred for 24 h at room temperature. Finally, water (50 mL) was added, the precipitate was collected by filtration and dried to give the crude product mixture.

Recrystallized from a mixture of diisopropyl ether (10 mL) and ethyl acetate (6 mL); off-white crystals; mp: 149-151°C (degr.); yield: 47%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.89 (d, 1H, H4, J=1.5 Hz), 8.09 (dd, 1H, H6, J=6.8, 1.5 Hz), 7.62-7.54 (m, 3H, arom. H), 7.39-7.32 (AA'BB', 2H, arom. H), 5.60 (s, 2H, CH_2), 2.84 (q, 2H, CH_2, J=7.5 Hz), 1.30 (t, 3H, CH_3, J=7.5 Hz).

Example 44

Preparation Of 5-(4-Bromobenzyl)-2-(2-chlorophenyl)-5*H*-imidazo[4,5-c]pyridine (GPJN-54)

A mixture of the 3,4-diaminopyridine (1.00 g), 2-chlorobenzoic acid (1 equivalent) and polyphosphoric acid (25 g) was heated at 190°C for 3 h with stirring. Then the mixture was cooled to ambient temperature and poured into ice/water. The resulting mixture was made alkaline by addition of 2N NaOH and the resulting precipitate was collected by filtration and dried. The crude product was recrystallized from a mixture of water (100 mL) and ethanol (17 mL) to give 67% of 2-(2-chlorophenyl)-1(3)*H*-imidazo[4,5-c]pyridine as an off-white powder.

2-(2-Chlorophenyl)-1(3)*H*-imidazo[4,5-c]pyridine (0.383 g) was dissolved in dry DMF (10 mL) and the resulting solution was cooled to 0°C. Aqueous 33% sodium hydroxide (1.5 equivalents) was added and the mixture was stirred for 15 min. Then 4-bromobenzyl bromide (1.2 equivalents) was added portionwise and the resulting mixture was stirred for 24 h at room temperature. Finally, water (80 mL) was added, the precipitate was collected by filtration and dried to give the crude product.

Recrystallized from a mixture of diisopropyl ether (20 mL) and ethyl acetate (25 mL); pale orange powder; mp: 190-192°C; yield: 33%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.21 (d, 1H, H4, J=1.6 Hz), 8.22 (dd, 1H, H6, J=6.8, 1.6 Hz), 8.09-8.02 (m, 1H, arom. H), 7.80 (d, 1H, H7, J=6.8 Hz), 7.65-7.51 (m, 3H, arom. H), 7.46-7.38 (m, 4H, arom. H), 5.67 (s, 2H, CH_2).

Example 45

Preparation Of 5-(4-Bromobenzyl)-2-(3-chlorophenyl)-5*H*-imidazo[4,5-c]pyridine (GPJN-55)

A mixture of the 3,4-diaminopyridine (1.00 g), 3-chlorobenzoic acid (1 equivalent) and polyphosphoric acid (25 g) was heated at 190°C for 3 h with stirring. Then the mixture was cooled to ambient temperature and poured into ice/water. The resulting mixture was made alkaline by addition of 2N NaOH and the resulting precipitate was collected by filtration and dried. The crude product was recrystallized from a mixture of water (100 mL) and ethanol (180 mL) to give 63% of 2-(3-chlorophenyl)-1(3)*H*-imidazo[4,5-c]pyridine as a white powder.

2-(3-Chlorophenyl)-1(3)*H*-imidazo[4,5-c]pyridine (0.383 g) was dissolved in dry DMF (10 mL) and the resulting solution was cooled to 0°C. Aqueous 33% sodium hydroxide (1.5 equivalents) was added and the mixture was stirred for 15 min. Then 4-bromobenzyl bromide (1.2 equivalents) was added portionwise and the resulting mixture was stirred for 24 h at room temperature. Finally, water (80 mL) was added, the precipitate was collected by filtration and dried to give the crude product.

Recrystallized from a mixture of diisopropyl ether (20 mL) and ethyl acetate (45 mL); colorless powder; mp: 155-157°C; yield: 42%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.16 (d, 1H, H4, J=1.5 Hz), 8.35-8.28 (m, 2H, arom. H), 8.20 (dd, 1H, H6, J=6.9, 1.5 Hz), 7.80 (d, 1H, H7, J=6.9 Hz), 7.64-7.38 (m, 6H, arom. H), 5.66 (s, 2H, CH_2).

Example 46

Preparation Of 5-(4-Bromobenzyl)-2-(4-chlorophenyl)-5*H*-imidazo[4,5-c]pyridine (GPJN-56)

A mixture of the 3,4-diaminopyridine (1.00 g), 4-chlorobenzoic acid (1 equivalent) and polyphosphoric acid (25 g) was heated at 190°C for 3 h with stirring. Then the mixture was cooled to ambient temperature and poured into ice/water. The resulting mixture was made alkaline by addition of 2N NaOH and the resulting precipitate was collected by filtration and dried. The crude product was recrystallized from a mixture of water (100 mL) and ethanol (110 mL) to give 47% of 2-(4-chlorophenyl)-1(3)*H*-imidazo[4,5-c]pyridine as a colorless powder.

2-(4-Chlorophenyl)-1(3)*H*-imidazo[4,5-c]pyridine (0.383 g) was dissolved in dry DMF (10 mL) and the resulting solution was cooled to 0°C. Aqueous 33% sodium hydroxide (1.5 equivalents) was added and the mixture was stirred for 15 min. Then 4-bromobenzyl bromide (1.2 equivalents) was added portionwise and the resulting mixture was stirred for 24 h at room temperature. Finally, water (80 mL) was added, the precipitate was collected by filtration and dried to give the crude product.

Recrystallized from a mixture of diisopropyl ether (20 mL) and ethyl acetate (25 mL); off-white powder; mp: 214-215°C; yield: 67%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.13 (d, 1H, H4, J=1.6 Hz), 8.39-8.32 (AA'BB', 2H, arom. H), 8.18 (dd, 1H, H6, J=6.9, 1.6 Hz), 7.64-7.58 (AA'BB', 2H, arom. H), 7.56-7.49 (AA'BB', 2H, arom. H), 7.44-7.38 (AA'BB', 2H, arom. H), 5.65 (s, 2H, CH_2).

Example 47

Preparation Of 5-(4-Bromobenzyl)-2-(2-pyridyl)-5*H*-imidazo[4,5-c]pyridine (GPJN-58)

A mixture of the 3,4-diaminopyridine (1.00 g), picolinic acid (1 equivalent) and polyphosphoric acid (25 g) was heated at 190°C for 3 h with stirring. Then the mixture was cooled to ambient temperature and poured into ice/water. The resulting mixture was made alkaline by addition of solid NaOH and the resulting precipitate was collected by filtration and dried. The crude product was recrystallized from a mixture of water (50 mL) and ethanol (7 mL) to give 55% of 2-(2-pyridyl)-1(3)*H*-imidazo[4,5-c]pyridine as an off-white powder.

2-(2-Pyridyl)-1(3)*H*-imidazo[4,5-c]pyridine (0.327 g) was dissolved in dry DMF (10 mL) and the resulting solution was cooled to 0°C. Aqueous 33% sodium hydroxide (1.5 equivalents) was added and the mixture was stirred for 15 min. Then 4-bromobenzyl bromide (1.2 equivalents) was added portionwise and the resulting mixture was stirred for 24 h at room temperature. Finally, water (80 mL) was added, the precipitate was collected by filtration and dried to give the crude product.

Recrystallized from a mixture of ethyl acetate (75 mL) and ethanol (10 mL); pale brown crystals; mp: 256-258°C; yield: 43%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.21 (d, 1H, H4, J=1.4 Hz), 8.68 (ddd, 1H, pyridine-H6), 8.40 (ddd, 1H, pyridine-H), 8.20 (dd, 1H, H6, J=6.8,

1.4 Hz), 7.89 (ddd, H, pyridine-H), 7.79 (d, 1H, H7, J=6.8 Hz), 7.65-7.58 (AA'BB', 2H, arom. H), 7.45-7.37 (m, 3H, arom. H), 5.68 (s, 2H, CH_2).

Example 48

Preparation Of 5-(4-Bromobenzyl)-2-(3-pyridyl)-5*H*-imidazo[4,5-c]pyridine (GPJN-57)

A mixture of the 3,4-diaminopyridine (1.00 g), nicotinic acid (1 equivalent) and polyphosphoric acid (25 g) was heated at 190°C for 3 h with stirring. Then the mixture was cooled to ambient temperature and poured into ice/water. The resulting mixture was made alkaline by addition of solid NaOH and the resulting solution was evaporated. The residue was extracted twice with ethyl acetate (2 x 200 mL) and the combined organic phases were dried (Na_2SO_4) and evaporated. The crude product, thus obtained, was recrystallized from a mixture of ethyl acetate (50 mL) and ethanol (13 mL) to give 34% of 2-(3-pyridyl)-1(3)*H*-imidazo[4,5-c]pyridine as an off-white powder.

2-(3-Pyridyl)-1(3)*H*-imidazo[4,5-c]pyridine (0.327 g) was dissolved in dry DMF (10 mL) and the resulting solution was cooled to 0°C. Aqueous 33% sodium hydroxide (1.5 equivalents) was added and the mixture was stirred for 15 min. Then 4-bromobenzyl bromide (1.2 equivalents) was added portionwise and the resulting mixture was stirred for 24 h at room temperature. Finally, water (80 mL) was added, the precipitate was collected by filtration and dried to give the crude product.

Recrystallized from a mixture of diisopropyl ether (10 mL), ethyl acetate (75 mL) and ethanol (20 mL); pale yellow powder; mp: 270-272°C; yield: 40%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.49 (m, 1H, pyridine-H2), 9.18 (d, 1H, H4, J=1.5 Hz), 8.65-8.60 (m, 2H, arom. H), 8.21 (dd, 1H, H6, J=6.8, 1.5 Hz), 7.79 (d, 1H, H7, J=6.8 Hz), 7.65-7.58 (AA'BB', 2H, arom. H), 7.54-7.38 (m, 3H, arom. H), 5.66 (s, 2H, CH_2).

Example 49

Preparation Of 5-(4-Bromobenzyl)-2-(4-pyridyl)-5*H*-imidazo[4,5-c]pyridine (GPJN-49)

A mixture of the 3,4-diaminopyridine (1.00 g), isonicotinic acid (1 equivalent) and polyphosphoric acid (25 g) was heated at 190°C for 3 h with stirring. Then the mixture was cooled to ambient temperature and poured into ice/water. The resulting mixture was made

alkaline by addition of solid NaOH and the resulting precipitate was collected by filtration and dried. The crude product was recrystallized from water (55 mL) to give 84% of 2-(4-pyridyl)-1(3)*H*-imidazo[4,5-c]pyridine as a pale orange powder.

2-(4-Pyridyl)-1(3)*H*-imidazo[4,5-c]pyridine (0.327 g) was dissolved in dry DMF (11 mL) and the resulting solution was cooled to 0°C. Aqueous 33% sodium hydroxide (1.5 equivalents) was added and the mixture was stirred for 15 min. Then 4-bromobenzyl bromide (1.2 equivalents) was added portionwise and the resulting mixture was stirred for 24 h at room temperature. Finally, water (80 mL) was added, the precipitate was collected by filtration and dried to give the crude product.

Recrystallized from a mixture of diisopropyl ether (10 mL) and ethyl acetate (75 mL); pale brown powder; mp: 190-194°C (degr.); yield: 40%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.25 (d, 1H, H4, J=1.4 Hz), 8.70-8.67 (m, 2H, pyridine-H2/6), 8.25-8.20 (m, 3H, arom. H), 7.83 (d, 1H, H7, J=6.8 Hz), 7.64-7.58 (AA'BB', 2H, arom. H), 7.45-7.39 (AA'BB', 2H, arom. H), 5.68 (s, 2H, CH_2).

Example 50

Preparation Of 5-(4-Bromobenzyl)-2-(2-thienyl)-5*H*-imidazo[4,5-c]pyridine (GPJN-53)

A mixture of the 3,4-diaminopyridine (1.00 g), thiophene-2-carboxylic acid (1 equivalent) and polyphosphoric acid (25 g) was heated at 190°C for 3 h with stirring. Then the mixture was cooled to ambient temperature and poured into ice/water. The resulting mixture was neutralized by addition of solid NaOH and the resulting precipitate was collected by filtration and dried. The crude product was recrystallized from a mixture of water (50 mL) and ethanol (25 ml) to give 30% of 2-(2-thienyl)-1(3)*H*-imidazo[4,5-c]pyridine as pale yellow crystals.

2-(2-Thienyl)-1(3)*H*-imidazo[4,5-c]pyridine (0.335 g) was dissolved in dry DMF (10 mL) and the resulting solution was cooled to 0°C. Aqueous 33% sodium hydroxide (1.5 equivalents) was added and the mixture was stirred for 15 min. Then 4-bromobenzyl bromide (1.2 equivalents) was added portionwise and the resulting mixture was stirred for 24 h at room temperature. Finally, water (80 mL) was added, the precipitate was collected by filtration and dried to give the crude product.

Recrystallized from ethyl acetate (70 mL); pale yellow powder; mp: 230-231°C; yield: 24%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.01 (d, 1H, H4, J=1.5 Hz), 8.16 (dd, 1H, H6, J=6.8, 1.5 Hz), 7.81 (dd, 1H, thiophene-H, J=3.6, 1.4 Hz), 7.67 (d, 1H, H7, J=6.8 Hz), 7.64-7.57 (m, 3H, arom. H), 7.43-7.37 (AA'BB', 2H, arom. H), 5.63 (s, 2H, CH_2).

Example 51

Preparation Of 2-Benzyl-5-(4-bromobenzyl)-5*H*-imidazo[4,5-c]pyridine (GPJN-67)

A mixture of the 3,4-diaminopyridine (1.00 g), phenylacetic acid (1 equivalent) and polyphosphoric acid (25 g) was heated at 120°C for 1 h and then at 150°C for 12 h with stirring. Then the mixture was cooled to ambient temperature and poured into ice/water. The resulting mixture was made alkaline by addition of solid NaOH and the resulting precipitate was collected by filtration and dried. The crude product was recrystallized from a mixture of diisopropyl ether (20 mL) and ethyl acetate (76 mL) to give 57% of 2-benzyl-1(3)*H*-imidazo[4,5-c]pyridine as a colorless powder.

2-Benzyl-1(3)*H*-imidazo[4,5-c]pyridine (0.500 g) was dissolved in dry DMF (5 mL) and the resulting solution was cooled to 0°C. Aqueous 33% sodium hydroxide (1.5 equivalents) was added and the mixture was stirred for 15 min. Then 4-bromobenzyl bromide (1.2 equivalents) was added portionwise and the resulting mixture was stirred for 24 h at room temperature. Finally, water (80 mL) was added, the precipitate was collected by filtration and dried to give the crude product.

Recrystallized from a mixture of ethyl acetate (50 mL) and ethanol (6.5 mL); pale yellow powder; mp: 232-233°C; yield: 46%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.94 (d, 1H, H4, J=1.4 Hz), 8.10 (dd, 1H, H6, J=6.8, 1.4 Hz), 7.61-7.39 (m, 3H, arom. H), 7.38-7.10 (m, 7H, arom. H), 5.65 (s, 2H, 5-CH_2), 4.17 (s, 2H, 2-CH_2).

Example 52

Preparation Of 5-(4-Bromobenzyl)-2-(1-naphthyl)-5*H*-imidazo[4,5-c]pyridine (GPJN-62)

A mixture of the 3,4-diaminopyridine (1.00 g), 1-naphthoic acid (1 equivalent) and polyphosphoric acid (25 g) was heated at 190°C for 3 hours with stirring. Then the mixture

was cooled to ambient temperature and poured into ice/water. The resulting mixture was made alkaline by addition of solid NaOH and the resulting precipitate was collected by filtration and dried. The crude product was recrystallized from a mixture of water (100 mL) and ethanol (130 mL) to give 47% of 2-(1-naphthyl)-1(3)*H*-imidazo[4,5-c]pyridine as an off-white powder.

2-(1-Naphthyl)-1(3)*H*-imidazo[4,5-c]pyridine (0.409 g) was dissolved in dry DMF (10 mL) and the resulting solution was cooled to 0°C. Aqueous 33% sodium hydroxide (1.5 equivalents) was added and the mixture was stirred for 15 min. Then 4-bromobenzyl bromide (1.2 equivalents) was added portionwise and the resulting mixture was stirred for 24 h at room temperature. Finally, water (80 mL) was added, the precipitate was collected by filtration and dried to give the crude product.

Recrystallized from a mixture of diisopropyl ether (10 mL), ethyl acetate (50 mL) and ethanol (5 mL); pale yellow powder; mp: 210-213°C (degr.); yield: 22%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.73 (m, 1H, arom. H), 9.22 (d, 1H, H4, J=1.6 Hz), 8.52 (dd, 1H, arom. H, J=7.2, 1.4 Hz), 8.23 (dd, 1H, H6, J=6.8, 1.6 Hz), 8.03-7.95 (m, 2H, arom. H), 7.83 (d, 1H, H7, J=6.8 Hz), 7.65-7.41 (m, 7H, arom. H), 5.68 (s, 2H, CH_2).

Example 53

Preparation Of 5-(4-Bromobenzyl)-2-(2-naphthyl)-5*H*-imidazo[4,5-c]pyridine (GPJN-63)

A mixture of the 3,4-diaminopyridine (1.00 g), 2-naphthoic acid (1 equivalent) and polyphosphoric acid (25 g) was heated at 190°C for 3 hours with stirring. Then the mixture was cooled to ambient temperature and poured into ice/water. The resulting mixture was made alkaline by addition of solid NaOH and the resulting precipitate was collected by filtration and dried. The crude product was recrystallized from a mixture of water (100 mL) and ethanol (400 mL) to give 28% of 2-(2-naphthyl)-1(3)*H*-imidazo[4,5-c]pyridine as an off-white powder.

2-(2-Naphthyl)-1(3)*H*-imidazo[4,5-c]pyridine (0.409 g) was dissolved in dry DMF (10 mL) and the resulting solution was cooled to 0°C. Aqueous 33% sodium hydroxide (1.5 equivalents) was added and the mixture was stirred for 15 min. Then 4-bromobenzyl bromide (1.2 equivalents) was added portionwise and the resulting mixture was stirred for 24 h at room

temperature. Finally, water (80 mL) was added, the precipitate was collected by filtration and dried to give the crude product.

Recrystallized from a mixture of diisopropyl ether (20 mL) and ethyl acetate (60 mL); pale orange powder; mp: 133-138°C (degr.); yield: 52%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.13 (d, 1H, H4, J=1.4 Hz), 8.93 (br s, 1H, arom. H), 8.51 (dd, 1H, arom. H, J=8.6, 1.6 Hz), 8.19 (dd, 1H, H6, J=6.7, 1.4 Hz), 8.10-7.90 (m, 3H, arom. H), 7.76 (d, 1H, H7, J=6.7 Hz), 7.65-7.50 (m, 4H, arom. H), 7.52-7.39 (AA'BB', 2H, arom. H), 5.67 (s, 2H, CH_2).

PART B

Example 54

Anti-BVDV (strain PE515) activity in MDBK cells

Compound	example	EC_{50} (µg/ml)	CC_{50} (µg/ml)	SI
GPJN-1	4	0.240	> 83.3	>345
GPJN-2	7	>100	>100	1
GPJN-3	5	0.060	60	1003
GPJN-4	6	0.040	46	1144
GPJN-7	9	0.042	22	525
GPJN-8	10	0.086	51	592
GPJN-9	11	0.049		
GPJN-9 xHCl	25	0.016		
GPJN-11	12	0.032	36	1135
GPJN-12	13	0.059	56	949
GPJN-13	14	0.043	45	1058
GPJN-14	8	0.070	40	573
GPJN-15	17	0.009	29	3079
GPJN-16	21	0.246	8,1	33
GPJN-17	18	0.097	50	517
GPJN-18	19	0.019	55	2933
GPJN-19	20	0.013	40	3012
GPJN-20	15	0.165	28	169
GPJN-21	16	0.022	22	1020
GPJN-22	22	0.029	13	450
GPJN-23	23	0.014	46	3230
GPJN-24	24	0.040	21	519

GPJN-25	26	0.009	36	4138
GPJN-26	27	0.041	>100	>2439
GPJN-27	28	0.945	>46	>48
GPJN-28	29	0.325	>75	>230
GPJN-29	30	5.330	>100	>18
GPJN-30	31	1.130	>50	>44
GPJN-31	32	0.455	>100	>222
GPJN-32	35	0.027	20	741
GPJN-33	36	0.200	70	350
GPJN-34	33	0.865	>100	>116
GPJN-35	34	0.365	>100	>273
GPJN-36	37	0.019	24	1297
GPJN-37	38	0.161	22	137
GPJN-38	39	0.235	50	213
GPJN-39	40	0.245	>100	>408
GPJN-40	41	0.250	>100	>400
GPJN-41	42	0.580	>100	>172
GPJN-48	43	0.351	>100	>285
GPJN-49	49	0.180	62	344
GPJN-50		0.021	>100	4760
GPJN-53	50	0.033	66	2028
GPJN-54	44	0.100	35	349
GPJN-55	45	0.060	>100	>1666
GPJN-56	46	2.205	>100	>45
GPJN-57	48	2.005	>100	>50
GPJN-58	47	0.052	8,1	156
GPJN-60		0.015	>77	5133
GPJN-62	52	0.120	9,4	78
GPJN-63	53	0.0042	4.3	1023
GPJN-64		0.026	>100	3846
GPJN-65		0.01	>100	10.000
GPJN-67	51	>100	>100	>100
GPJN-68		0.026	17	653
GPJN-73		0.017	>100	5882
GPJN-75		0.018	31.7	1761
GPJN-79		0.083	>100	1204
GPJN-80		0.18	>100	555
GPRTI-8	3	0.137	>79	>576
VP32947**		0.003	47	>16785

** *Baginsky et al., Proc Natl Acad Sci U S A 2000 Jul 5;97(14):7981-6*

EC_{50}: effective concentration required to reduce virus induced cytopathic effect in MDBK cells by 50%.

IC_{50}: inhibitory concentration required to reduce the growth of exponentially growing MDBK cells by 50%

SI: IC_{50}/EC_{50}.

5 *Data are mean values for 2-5 independent determinations*

Example 55

Anti-coxsackie B3 activity in Vero cells

Compound	example	EC_{50} (µg/ml)	TC_{50} (µg/ml)	SI
GPJN-5		6.0	>100	16.6
GPJN-32	35	6.5	69	15.4
GPJN-40	41	8.95	>100	11.2
GPJN-50		8.47	>100	11.8
GPJN-60		6.1	>100	16.4
GPJN-64		12	>42	3.5
GPRTI-8	3	12.2	>100	8.48

EC_{50}: effective concentration required to reduce virus (CBV-3 Nancy strain)-induced cytopathic effect in Vero cells by 50%.

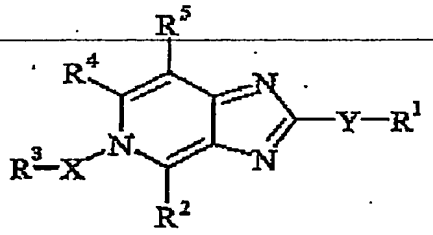
TC_{50}: effective concentration required to reduce the metabolism of confluent Vero cells by 50% as determined by the MTS method.

SI: IC_{50}/EC_{50}.

Data are mean values for two or more independent determinations

CLAIMS

1. A compound according to formula I



I

or a pharmaceutically acceptable salt thereof, wherein

R^1 is selected from hydrogen; phenyl substituted with 0-3 R^6; (benzoannellated) 5 or 6 membered heterocyclic ring containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^6; 1-naphthyl substituted with 0-3 R^6; 2-naphthyl substituted with 0-3 R^6; C_{3-7} cycloalkyl; C_{5-7} cycloalkenyl with the proviso that the double bond cannot be adjacent to a nitrogen.

Y is selected from the group $-(CH_2)_{0-5}-$; O; S; NR^{11}; $-CH(CH_3)-$; $-OCH_2-$; $-CH_2O-$; $-OCH_2-CH_2-$; $-CH_2-CH_2O-$; $-CH_2-O-CH_2-$; $-SCH_2-$; $-CH_2S-$; $-SCH_2-CH_2-$; $-CH_2-CH_2S-$; $-CH_2-S-CH_2-$; $-NR^{11}-CH_2-$; $-CH_2-NR^{11}-$; $-NR^{11}-CH_2-CH_2-$; $-CH_2-CH_2-NR^{11}-$; $-CH_2-NR^{11}-CH_2-$; $-C(CH_3)_2-$; (cis or trans) $-CH=CH-$; (cis or trans) $-CH_2-CH=CH-$; (cis or trans) $-CH=CH-CH_2-$.

R^2, R^4 and R^5 are independently selected from hydrogen; straight or branched C_{1-6} alkoxy; straight or branched C_{1-6} alkyl; F; Cl; Br; I; OH; CN; NO_2; NR^7R^8; OCF_3; CF_3; $C(=O)R^9$; phenyl; phenoxy; benzyl; hydroxymethyl.

X is selected from the group $-CH_2-$; $-CH(CH_3)-$; $-CH_2-CH_2-$; $-CH_2-CH_2-CH_2-$; $-CH_2-CH_2-CH_2-CH_2$; $-OCH_2-CH_2-$; $-SCH_2-CH_2-$; $-NR^{10}-CH_2-CH_2-$; C_{3-7} cycloalkylidene; $-C(CH_3)_2-$; $-CH_2-CH(CH_3)-CH_2-$; $-CH(CH_3)-CH_2-CH_2-$; $-CH_2-CH_2-CH(CH_3)-$; $-CH=CH-CH_2-$.

R^3 is selected from phenyl substituted with 0-3 R^{17}; (benzoannellated) 5 or 6 membered heterocyclic ring containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^{17}; 1-naphthyl substituted with 0-3 R^{17}; 2-naphthyl substituted with 0-3 R^{17}; C_{3-7} cycloalkyl; C_{5-7} cycloalkenyl with the proviso that the double bond cannot be adjacent to a nitrogen.

R^6 and R^{17} are independently selected from the group H; straight or branched C_{1-6} alkoxy; straight or branched C_{1-6} alkyl; F; Cl; Br; I; OH; CN; NO_2; $NR^{13}R^{14}$; OCF_3; CF_3; $C(=O)R^{18}$; phenyl; phenoxy; benzyl; hydroxymethyl.

R^7 and R^8 are independently selected from H; straight or branched C_{1-6} alkyl; phenyl; $C(=O)R^{12}$.

alternatively, R^7 and R^8, together with the nitrogen to which they are attached, combine to form a 5-6 membered ring containing 0-1 O or N atoms.

R^9 and R^{18} are independently selected from H; OH; straight or branched C_{1-6} alkyl; straight or branched C_{1-6} alkoxy; $NR^{15}R^{16}$; phenyl.

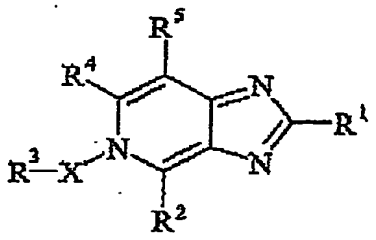
R^{10} and R^{11} are independently selected from the group H; C_{1-6} straight or branched alkyl; phenyl.

R^{12} is selected from the group H; C_{1-6} straight or branched alkyl; phenyl.

R^{13} and R^{14} are independently selected from H; straight or branched C_{1-6} alkyl; phenyl; $C(=O)R^{12}$.

R^{15} and R^{16} are independently selected from the group H; C_{1-6} straight or branched alkyl; phenyl.

2. A compound according to formula II



II

or a pharmaceutically acceptable salt thereof, wherein

R^1 is selected from phenyl substituted with 0-3 R^6; (benzoannellated) 5 or 6 membered heterocyclic ring containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^6; 1-naphthyl substituted with 0-3 R^6; 2-naphthyl substituted with 0-3 R^6; C_{3-7} cycloalkyl; C_{5-7} cycloalkenyl.

R^2, R^4 and R^5 are independently selected from hydrogen; straight or branched C_{1-6} alkoxy; straight or branched C_{1-6} alkyl; F; Cl; Br; I; OH; CN; NO_2; NR^7R^8; OCF_3; CF_3; $C(=O)R^9$; phenyl; phenoxy; benzyl; hydroxymethyl.

X is selected from the group $-CH_2-$; $-CH(CH_3)-$; $-CH_2-CH_2-$; $-CH_2-CH_2-CH_2-$; $-CH_2-CH_2-CH_2-CH_2$; $-OCH_2-CH_2-$; $-SCH_2-CH_2-$; $-NR^{10}-CH_2-CH_2-$; C_{3-7} cycloalkylidene; $-C(CH_3)_2-$; $-CH_2-CH(CH_3)-CH_2-$; $-CH(CH_3)-CH_2-CH_2-$; $-CH_2-CH_2-CH(CH_3)-$; $-CH=CH-CH_2-$.

R^3 is selected from phenyl substituted with 0-3 R^{17}; (benzoannellated) 5 or 6 membered aromatic heterocyclic ring containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^{17}; 1-naphthyl substituted with 0-3 R^{17}; 2-naphthyl substituted with 0-3 R^{17}; C_{3-7} cycloalkyl; C_{5-7} cycloalkenyl with the proviso that the double bond cannot be adjacent to a nitrogen.

R^6 and R^{17} are independently selected from the group H; straight or branched C_{1-6} alkoxy; straight or branched C_{1-6} alkyl; F; Cl; Br; I; OH; CN; NO_2; $NR^{13}R^{14}$; OCF_3; CF_3; $C(=O)R^{18}$; phenyl; phenoxy; benzyl; hydroxymethyl.

R^7 and R^8 are independently selected from H; straight or branched C_{1-6} alkyl; phenyl; $C(=O)R^{12}$.

alternatively, R^7 and R^8, together with the nitrogen to which they are attached, combine to form a 5-6 membered ring containing 0-1 O or N atoms.

R^9 and R^{18} are independently selected from H; OH; straight or branched C_{1-6} alkyl; straight or branched C_{1-6} alkoxy; $NR^{15}R^{16}$; phenyl.

R^{10} is selected from the group H; C_{1-6} straight or branched alkyl; phenyl.

R^{12} is selected from the group H; C_{1-6} straight or branched alkyl; phenyl.

R^{13} and R^{14} are independently selected from H; straight or branched C_{1-6} alkyl; phenyl; $C(=O)R^{12}$.

R^{15} and R^{16} are independently selected from the group H; C_{1-6} straight or branched alkyl; phenyl.

3. A compound according to claim 2, characterised in that

R^1 is selected from phenyl substituted with 0-3 R^6; (benzoannellated) 5 or 6 membered heterocyclic ring containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^6; 1-naphthyl substituted with 0-3 R^6; 2-naphthyl substituted with 0-3 R^6; C_{3-7} cycloalkyl; C_{5-7} cycloalkenyl.

R^2, R^4 and R^5 are independently selected from hydrogen; straight or branched C_{1-6} alkoxy; straight or branched C_{1-6} alkyl; F; Cl; Br; I; OH; CN; NO_2; NR^7R^8; OCF_3; CF_3; $C(=O)R^9$; phenyl; phenoxy; benzyl; hydroxymethyl.

X is selected from the group $-CH_2-$; $-CH(CH_3)-$; $-CH_2-CH_2-CH_2-$; $-OCH_2-CH_2-$; $-CH=CH-CH_2-$.

R^3 is selected from phenyl substituted with 0-3 R^{17}; (benzoannellated) 5 or 6 membered aromatic heterocyclic ring containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^{17}; 1-naphthyl substituted with 0-3 R^{17}; 2-naphthyl substituted with 0-3 R^{17}; C_{3-7} cycloalkyl; C_{5-7} cycloalkenyl with the proviso that the double bond cannot be adjacent to a nitrogen.

R^6 and R^{17} are independently selected from the group H; straight or branched C_{1-6} alkoxy; straight or branched C_{1-6} alkyl; F; Cl; Br; I; OH; CN; NO_2; $NR^{13}R^{14}$; OCF_3; CF_3; $C(=O)R^{18}$; phenyl; phenoxy; benzyl; hydroxymethyl.

R^7 and R^8 are independently selected from H; straight or branched C_{1-6} alkyl; phenyl; $C(=O)R^{12}$.

alternatively, R^7 and R^8, together with the nitrogen to which they are attached, combine to form a 5-6 membered ring containing 0-1 O or N atoms.

R^9 and R^{18} are independently selected from H; OH; straight or branched C_{1-6} alkyl; straight or branched C_{1-6} alkoxy; $NR^{15}R^{16}$; phenyl.

R^{12} is selected from the group H; C_{1-6} straight or branched alkyl; phenyl.

R^{13} and R^{14} are independently selected from H; straight or branched C_{1-6} alkyl; phenyl; $C(=O)R^{12}$.

R^{15} and R^{16} are independently selected from the group H; C_{1-6} straight or branched alkyl; phenyl.

4. A compound according to claim 2, characterised in that

R^1 is selected from phenyl substituted with 0-3 R^6; (benzoannellated) 5 or 6 membered heterocyclic ring containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^6; 1-naphthyl substituted with 0-3 R^6; 2-naphthyl substituted with 0-3 R^6; C_{3-7} cycloalkyl; C_{5-7} cycloalkenyl.

R^2, R^4 and R^5 are hydrogen.

X is selected from the group $-CH_2-$; $-CH(CH_3)-$; $-CH_2-CH_2-CH_2-$; $-OCH_2-CH_2-$; $-CH=CH-CH_2-$.

R^3 is selected from phenyl substituted with 0-3 R^{17}; (benzoannellated) 5 or 6 membered aromatic heterocyclic ring containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^{17}; 1-naphthyl substituted with 0-3 R^{17}; 2-naphthyl substituted with 0-3 R^{17}; C_{3-7} cycloalkyl; C_{5-7} cycloalkenyl with the proviso that the double bond cannot be adjacent to a nitrogen.

R^6 and R^{17} are independently selected from the group H; straight or branched C_{1-6} alkoxy; straight or branched C_{1-6} alkyl; F; Cl; Br; I; OH; CN; NO_2; $NR^{13}R^{14}$; OCF_3; CF_3; $C(=O)R^9$; phenyl; phenoxy; benzyl; hydroxymethyl.

R^9 is selected from H; OH; straight or branched C_{1-6} alkyl; straight or branched C_{1-6} alkoxy; $NR^{15}R^{16}$; phenyl.

R^{13} and R^{14} are independently selected from H; straight or branched C_{1-6} alkyl; phenyl; $C(=O)R^{12}$.

R^{15} and R^{16} are independently selected from the group H; C_{1-6} straight or branched alkyl; phenyl.

5. A compound according to claim 2, characterised in that

R^1 is selected from phenyl substituted with 0-3 R^6; (benzoannellated) 5 or 6 membered heterocyclic ring containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^6; 1-naphthyl substituted with 0-3 R^6; 2-naphthyl substituted with 0-3 R^6.

R^2, R^4 and R^5 are hydrogen.

X is selected from $-CH_2-$; $-CH(CH_3)-$; $-CH_2-CH_2-CH_2-$; $-OCH_2-CH_2-$; $-CH=CH-CH_2-$.

R^3 is selected from phenyl substituted with 0-3 R^{17}; (benzoannellated) 5 or 6 membered aromatic heterocyclic ring containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^{17}; 1-naphthyl substituted with 0-3 R^{17}; 2-naphthyl substituted with 0-3 R^{17}.

R^6 and R^{17} are independently selected from the group H; straight or branched C_{1-6} alkoxy; straight or branched C_{1-6} alkyl; F; Cl; Br; I; OH; CN; NO_2; $NR^{13}R^{14}$; OCF_3; CF_3; $C(=O)R^9$; phenyl; phenoxy; benzyl; hydroxymethyl.

R^9 is selected from H; OH; straight or branched C_{1-6} alkyl; straight or branched C_{1-6} alkoxy; $NR^{15}R^{16}$; phenyl.

R^{13} and R^{14} are independently selected from H; straight or branched C_{1-6} alkyl; phenyl; $C(=O)R^{12}$.

R^{15} and R^{16} are independently selected from the group H; C_{1-6} straight or branched alkyl; phenyl.

6. A compound according to claim 2, characterised in that

R^1 is selected from phenyl substituted with 0-3 R^6; 5 or 6 membered heterocyclic ring containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^6; 1-naphthyl substituted with 0-3 R^6; 2-naphthyl substituted with 0-3 R^6.

R^2, R^4 and R^5 are hydrogen.

X is selected from $-CH_2-$; $-CH(CH_3)-$; $-CH_2-CH_2-CH_2-$; $-OCH_2-CH_2-$; $-CH=CH-CH_2-$.

R^3 is selected from phenyl substituted with 0-3 R^{17}; 5 or 6 membered aromatic heterocyclic ring containing 1-3 heteroatoms selected from the group O, N, and S, substituted with 0-2 R^{17}; 1-naphthyl substituted with 0-3 R^{17}; 2-naphthyl substituted with 0-3 R^{17}.

R^6 and R^{17} are independently selected from hydrogen; straight or branched C_{1-6} alkoxy; straight or branched C_{1-6} alkyl; F; Cl; Br; I; OH; CN; NO_2; $NR^{13}R^{14}$; OCF_3; CF_3; $C(=O)R^9$; phenyl; phenoxy; benzyl; hydroxymethyl.

R^9 is selected from H; OH; straight or branched C_{1-6} alkyl; straight or branched C_{1-6} alkoxy; $NR^{15}R^{16}$; phenyl.

R^{13} and R^{14} are independently selected from H; straight or branched C_{1-6} alkyl; phenyl; $C(=O)R^{12}$.

R^{15} and R^{16} are independently selected from the group H; C_{1-6} straight or branched alkyl; phenyl.

7. A compound according to claim 1 or claim 2 selected of the group of

5-(2,6-Difluorobenzyl)-2-(2,6-difluorophenyl)-5*H*-imidazo[4,5-c]pyridine;
5-Benzyl-2-(2,6-difluorophenyl)-5*H*-imidazo[4,5-c]pyridine;
5-(2,6-Difluorobenzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine;
5-Benzyl-2-phenyl-5*H*-imidazo[4,5-c]pyridine;
2-(2,6-Difluorophenyl)-5-phenethyl-5*H*-imidazo[4,5-c]pyridine;
2-Phenyl-5-(3-phenyl-propyl)-5*H*-imidazo[4,5-c]pyridine;
5-(2-Chlorobenzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine;
5-(3-Chlorobenzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine;
5-(4-Chlorobenzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine;
5-(2-Methoxybenzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine;
5-(3-Methoxybenzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine;
5-(4-Methoxybenzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine;
5-(4-Methylbenzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine;
5-(3-Fluorobenzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine;
5-(4-Fluorobenzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine;
5-(4-Bromobenzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine;
4-(2-Phenyl-5*H*-imidazo[4,5-c]pyridin-5-ylmethyl)-benzonitrile;
5-(4-Trifluoromethyl-benzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine;
5-(4-Chlorobenzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine hydrochloride;
5-(5-Chloro-2-thienylmethyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine;

5-(2-Naphthylmethyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine;
2-Phenyl-5-(4-phenyl-butyl)-5*H*-imidazo[4,5-c]pyridine;
2-Phenyl-5-(4-phenyl-benzyl)-5*H*-imidazo[4,5-c]pyridine;
(R/S)-2-Phenyl-5-(1-phenyl-ethyl)-5*H*-imidazo[4,5-c]pyridine;
5-(1-Naphthylmethyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine;
5-(2,4-Difluorobenzyl)-2-(2,6-difluorophenyl)-5*H*-imidazo[4,5-c]pyridine;
5-(4-Bromobenzyl)-2-(2-chlorophenyl)-5*H*-imidazo[4,5-c]pyridine;
5-(4-Bromobenzyl)-2-(3-chlorophenyl)-5*H*-imidazo[4,5-c]pyridine;
5-(4-Bromobenzyl)-2-(4-chlorophenyl)-5*H*-imidazo[4,5-c]pyridine;
5-(4-Bromobenzyl)-2-(2-pyridyl)-5*H*-imidazo[4,5-c]pyridine;
5-(4-Bromobenzyl)-2-(2-thienyl)-5*H*-imidazo[4,5-c]pyridine;
5-(4-Bromobenzyl)-2-(1-naphthyl)-5*H*-imidazo[4,5-c]pyridin;
5-(4-Bromobenzyl)-2-(2-naphthyl)-5*H*-imidazo[4,5-c]pyridine;
5-(4-Iodobenzyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine;
5-(4-Bromobenzyl)-2-(3-fluorophenyl)-5*H*-imidazo[4,5-c]pyridine;
5-(4-Bromobenzyl)-2-(3-methylphenyl)-5*H*-imidazo[4,5-c]pyridine;
5-(4-Bromobenzyl)-2-(3-bromophenyl)-5*H*-imidazo[4,5-c]pyridine;
5-(4-Bromobenzyl)-2-(3-methoxyphenyl)-5*H*-imidazo[4,5-c]pyridine.
5-(4-Chlorobenzyl)-2-(3-bromophenyl)-5*H*-imidazo[4,5-c]pyridine;
5-(4-Chlorobenzyl)-2-(3-chlorophenyl)-5*H*-imidazo[4,5-c]pyridine;
5-(2-Phenoxy-ethyl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine;
5-(3-Phenyl-prop-2-en-1-yl)-2-phenyl-5*H*-imidazo[4,5-c]pyridine and
5-(4-Iodobenzyl)-2-(3-bromophenyl)-5*H*-imidazo[4,5-c]pyridine.

8. A compound according to any of claims 1 to 9 for use as a medicine.

9. A compound according to any of claims 1 to 9 for use as an antiviral agent.

10. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredient, a theurapeutically effective amount of a compound according to any of claims 1 to 9.

11. Us of a compound according to any of the claims 1 to 9 or a pharmaceutical composition according to claim 10 for the manufacture of a medicament in the treatment or prevention of viral infection

12. Us of a compound according to any of the claims 1 to 9 or a pharmaceutical composition according to claim 10 for the manufacture of a medicament in the treatment or prevention of a viral infection with a virus belonging to the family of the Flaviviridae.

13. Us of a compound according to any of the claims 1 to 9 or a pharmaceutical composition according to claim 10 for the manufacture of a medicament in the treatment or prevention of a viral infection with hepatitis-C-virus.

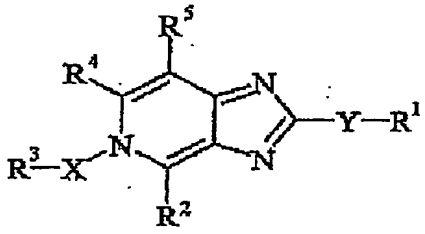
14. Us of a compound according to any of the claims 1 to 9 or a pharmaceutical composition according to claim 10 for the manufacture of a medicament in the treatment or prevention of a viral infection with a viruses belonging to the family of the Picornaviridae.

15. Us of a compound according to any of the claims 1 to 9 or a pharmaceutical composition according to claim 10 for the manufacture of a medicament in the treatment or prevention of a viral infection with a Coxsackie virus.

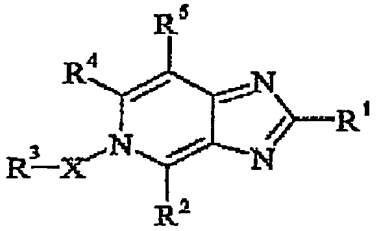
ABSTRACT

Viral inhibitors

The present inventions relates to a pharmaceutical composition for the treatment or prevention of viral infections comprising as an active principle at least one imidazo[4,5-c]pyridine derivative having the general formula (I) or (II)



I



II

The invention also relates to processes for the preparation of the compounds according to the invention having above mentioned general formula and their use as a medicine to treat or prevent viral infection.